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Editorial

Overview of high risk pregnancy

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With the changing demographics of Indian Population including increasing maternal age and weight during pregnancy, higher rates of pregnancies conceived by artificial technology and increasing number of caesarean section deliveries, complicated pregnancies have arisen.

High risk pregnancies may be simply classified any pregnancy in which there is a maternal or fetal factors that may adversely effect the outcome.

Many conditions may indirectly and truly intervened before or early in the perinatal period. When diagnosed through an appropriate method before pregnancy, conditions like Rh isoimmunisation, diabetes and epilepsy can be managed to minimise the risk of mortality and morbidity to both mother and baby.

However, it is not possible some other conditions like premature rupture of membrane, preeclampsia and premature rupture of membranes prior to pregnancy. To detect and manage these challenging situations, the obstetrician must maintain constant vigilance once pregnancy is established.

To tackle and manage this challenges obstetrician should keep constant vigilance. Many scientific breakthrough took place towards evaluation of fetal health and diseases in early 1960's.

In 1970's, the decade of perinatal medicine, paediatrician and obstetrician combined forces to continue improving perinatal survival.

In 1980's development of comprehensive evaluation of fetal condition with the biophysical profile, introduction of cordocentesis for diagnosis and therapy, the development of antenatal steroid therapy and antisurfactant with assisted reproductive technique facilitates to combat high risk pregnancy and to reduce the maternal and fetal mortality and morbidity rates.

Hence we can very precisely includes factor relating to high risk pregnancy and to treat properly.

(1) Maternal Nutrition :- #Increase body mass index, weight gain > adversely effect pregnancy outcome # Nutritional supplement like multivitamin, protein supplement, iron supplement, calcium, magnesium and vitamin D3> decreases the adverse effect.

Vitamin E Vitamin C and 3-N fatty acid> reduces preterm labour, preeclampsia thus having beneficial effect.

(2) Abuse of alcohol and substances:- Known to be detriment us to any pregnancies women aged 15-44 who have used alcohol (90%) and use substances like cocaine etc known to be indirect pregnancy outcome rate leading to IUGR, neonatal abstinence syndrome, fetal distress, preterm labour, still birth and sudden infant death syndrome,

(3) Environmental Agents and reproductive risk > principal of reproductive toxicities apply to environmental agents. A large proportion of adverse outcomes are unrelated to exposure. Only 5% of congenital malformations attributed to exposure to a chemical or pharmaceutical agent. Specific agent may be non toxic in low doses but toxic at higher doses. Such as X-ray exposure < 50 rad usually minor effects but >5 rad may be associated with microcephaly and mental retardation. The adverse effect thus relates to amount, time of exposure, amount absorb of different toxic agent. There are specific agents which is very much toxic to foetus mother like lead, mercury, pesticides, herbicides and Polychlorinated –diphenyls.

(4) Genetic Disorder > Genetic screening begins with an accurate family history, past history of still births and abortions including congenital malformation like cardiac defects, cleft lip and palate and neural tube defects. Genetic study should be done specifically in above mentioned factors and to avoid adverse pregnancy outcome like mendelian inheritance, hemoglobinopathies, cystic fibrosis etc.

(5) Maternal diseases like diabetes mellitus specially gestational diabetes, chronic renal disease, asthma, epilepsy, hypertension, immunological disease like SLE, HIV infections are the common and major factors/diseases needs vigilant obstetrical care where obstetrician should lead a team of speciality concern of the above diseases and a good team efforts will definitely reduce and minimise the adverse outcome of these high risk pregnancies.

India is advancing day by day in the field of obstetrics and with the help of higher sophisticated diagnostic tools and super specialise approach reduces markly the maternal and fetal mortality and morbidity particularly in high risk pregnancies.

Original Article

A survey on the line of management of myocardial infarction patients by the primary health care physicians in Puducherry

M Thulasimani[1], S Amarnath[2], S Ramaswamy[3], S Basalingappa[4], S Jaikumar[5], Arun Sharma[6]

Myocardial Infarction (MI) is the common cause of the mortality globally. If prompt treatment/referral is initiated within 90 minutes of development of infarction, the mortality rate can be minimized almost to 3%. Whenever patients develop any acute illness including chest pain, they usually attend the clinic of family physician first that are easily accessible to them. Therefore the role of family physician in management of MI is very significant. Hence a survey based on a validated questionnaire was conducted among general practitioners of Puducherry. It was observed from the survey that 93% of family physicians are aware of the importance of early administration of aspirin as a prehospital medication. However about 41% of physicians informed that they use enteric coated aspirin and not soluble aspirin. With regard to referring the patient for catheterization laboratory, 58% of physicians only felt that 3 hours as a maximum period. Only 21% of physicians preferred to use morphine as analgesic while the rest suggested drugs such as tramadol, diclofenac, aspirin, pentazocine, paracetamol and pethedine as alternatives to morphine. Most of physicians felt that non availability of morphine is due to stringent regulations and it is the main reason for not using the same. Streptokinase was preferred thrombolytic for 29% of physicians and tenecteplase was preferred by 35%.

From our present survey we feel that continuing medical education programs on MI pertaining to use of analgesics, referral time limit to Primary Percutaneous coronary intervention (PPCI) and use of most effective thrombolytic may be organized for primary care physicians so that timely management by them can reduce the mortality in MI significantly.

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Key words **: Myocardial Infarction, Primary Percutaneous coronary intervention**

Myocardial infarction (MI) is the common cause of mortality globally. A survey reveals that during the past few years the incidence of MI has reduced in western countries but an increase in the same in developing countries especially in India[1]. It has been documented beyond doubt that as much as 25% of patients who had MI die before reaching the tertiary health care centre. Therefore the present slogan of cardiologists with regard to management of MI is "Time is Myocardium". If prompt treatment/referral are initiated within 90 minutes of the development of infarction, the mortality rate can be minimized almost to 3%[2]. Whenever patients develop any acute illness including MI, they attend the clinics of family physicians first that are easily accessible to them. Hence, the role of family physicians in the management of MI is very significant. Appreciating the value of time and having an updated knowledge of management of MI, they can make immediate referral and save lives of MI patients.

Many times the family physicians are mislead by the wrong history provided by the patients that their spicy food might attribute to indigestion leading to the chest discomfort. Apart from this, any patient with chest pain should have an ECG which can mostly diagnose MI. Unfortunately, most of the patients are reluctant to undergo ECG test and request the family physicians to treat them with some injection emperically and inform them that they will come with ECG report next day morning. Unfortunately a significant proportion of these patients die before they could come for the next day to meet the family physician. Thus the family physicians to some extent are responsible for delay in treatment of MI. Hence, a duty is cast on fam-

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ily physicians to compel these patients to take ECG immediately which is affordable and easily accessible. It is also important that the treating family physicians should have knowledge of diagnosing MI from ECG so that they can initiate appropriate management. Unless they are aware of the update in management of MI such as immediate thrombolysis, angiogram followed by angioplasty, they may not be in a position to refer the patients in appropriate time. It was felt that a survey should be conducted on the line of management of MI by the primary health care physicians and hence the present survey has been undertaken.

Materials and Methods

A cross sectional survey was conducted with a validated questionnaire among family physicians of union territory of Puducherry from 20th January 2013 to 20th September 2013. The questionnaire was administered to 84 practicing family physicians randomly selected across Puducherry.

The salient features of the questionnaire included the information regarding:

- First line medication to be prescribed by them for suspected MI
- Use of morphine / alternate drug to morphine
- Use of aspirin and formulation of aspirin used
- Familiarity with ECG findings of MI
- Knowledge of latest treatment of MI

The practicing physicians were explained about the purpose of the study and informed consent was obtained. They were requested to complete the questionnaire and return it immediately. The data were analyzed and presented in the results.

Results

No	Questions	Responses	Percentage
1	If a patient with chest pain suspected as MI comes to your clinic, the first line of medication that you would prescribe before referring to a speciality centre.	Aspirin alone	16.66 %
		Aspirin + clopidogrel	11.90 %
		Aspirin+clopidogrel+statin	23.80 %
		Aspirin + nitrate	26.19 %
		Nitrate alone	16.66 %
		Morphine alone	4.76 %
2	Is morphine used in your clinic for acute MI	Yes	21.42 %
		No	78.57 %
3	If NO , alternate analgesic used in your clinic	Aspirin	24.24 %
		Tramadol	30.30 %
		Diclofenac	24.24 %
		Pentazocine	6.06 %
		Paracetamol	9.09 %
		Pethidine	6.06 %
4	Reason for non stocking of morphine in your clinic	Non availability	47.61 %
		Abuse / misuse	14.28 %
		Narcotic drug	9.52 %
		Legal issues	11.90 %
		Toxicity and side effects	4.76 %
		Don't want to take risk	2.38 %
		No response	9.52 %
5	Is Aspirin used in your clinic for acute MI	Yes	92.85 %
		No	7.14 %
6	If ,YES the type of Aspirin used	Soluble	58.97 %
		Enteric coated	41.02 %
7	Familiar with ECG findings of MI	Yes	90.47 %
		No	9.52 %
8	In case you are referring the patients mention the advice that you will give	Reassurance	14.28 %
		Immediate referral to a higher centre	47.61 %
		Aspirin	9.52 %
		Sublingual nitrates	9.52 %
		Oxygen therapy	14.28 %
9	In your opinion the latest treatment for MI is	Immediate thrombolysis with streptokinase	28.57 %
		Coronary angiogram followed by angioplasty in a nearby cardiac centre	33.33 %
		Referral to a corporate hospital with all facilities irrespective of distance	3.57 %
		Immediate thrombolysis with Tenecteplase	34.52 %
10	In your opinion what is the maximum period for the referral of patient to catheterization laboratory for angiography followed by angioplasty.	Within 3hours of the attack	58.33 %
		Within 6 hours of the attack	29.76 %
		Within 12 hours of the attack	9.52 %
		Within 24 hours of the attack	1.19 %

Discussion

The results reveal that 16.66 % of the family physicians preferred aspirin as first line medication for patients highly suspicious of MI. The choice to add clopidogrel along with aspirin was 11.90 %, nitrates with aspirin was 26.19% and clopidogrel and statins with aspirin were 23.80%. In all the three regimans aspirin found a place. Only 4.76 % of physicians preferred morphine alone where as 16.66 % preferred nitrates alone. It has been observed and suggested that administration of aspirin alone within 3 hours of occurrence of MI reduces the mortality rate in MI by 23%[3] and it is considered that the effect of timely administration of aspirin (which costs less than 50 paisa) is almost equal to the effect of streptokinase (which costs about not less than Rs 2,500 per vial). It is interesting to note that more than 75 % of physicians wanted to include aspirin as a primary drug with various combinations indicating their awareness of the life saving value of aspirin in management of MI.

With regard to use of morphine for MI patients in the clinic, 21.42 % of physicians informed that they use morphine and the remaining 78.57 % are not. The main reason for not using morphine by majority of physicians is essentially identified as non availability of morphine. Their prescriptions are not honoured. In addition to this, they don't want to face legal issues in view of the fact that the drug comes under the classification of narcotic and psychotropic substances. It is unfortunate that even though morphine is the most effective analgesic and by relieving pain it reduces the sympathetic activity, a vital role in management of MI, the patients are deprived of the benefits of morphine due to stringent drugs act. Hence, it is strongly felt that modalities to make morphine available to the primary care physicians requires immediate attention and should be considered as top priority by the drug controlling authorities. We also feel that national bodies like Indian Medical Association and Association of Physicians of India can address this issue to benefit the patients from excruciating severe pain of MI. It is heartening to note that a bill is likely to be passed in Loksabha for removing "out dated restriction on the use of morphine" as appeared in the editorial column of "The Hindu" dated 23rd august 2013.

In view of non availability of morphine as mentioned above, 30.30% of physicians preferred to use tramadol as an alternative analgesic. Tramadol is being used now as an alternative to morphine for treatment of post traumatic pain[4] but its safety of use in acute MI is not yet clearly known. Pentazocine was preferred by 6.06 %. Similar percentage of physicians preferred pethidine. However, pethidine is also not easily available. Further use of pentazocine in acute MI is not advised, as the hemodynamic effect of pentazocine make it unsuitable for use in MI.

Surprisingly 24.24 % of family physicians informed they use aspirin as alternative analgesic to morphine. Aspirin acts as analgesic at an ulcerogenic dose of 0.5 to 1gm. It acts as an anti platelet agent at a dose of 150 to 300 mg. If it is given in higher dose its anti platelet property may be lost and the purpose of using it in MI becomes meaningless. Further its analgesic potency cannot be compared with morphine to be used in MI. Injection diclofenac was chosen as alternative analgesic to morphine by 24.24% of physicians. Diclofenac is a non steroidal anti inflammatory drug useful in musculoskeletal pain and not in severe visceral pain; further the drug itself may reduce the anti platelet activity of aspirin. Moreover, patients with MI will be exposed to maximum stress leading to peptic ulcer. Diclofenac per se can either induce or potentiate the ulcer. The above discussed data warrants an urgent need for updating the analgesic use in MI by the family physicians.

Regarding the type of formulation of aspirin used for MI, 58.97% of physicians informed that they are using soluble aspirin while 41.02% are using enteric coated aspirin. As already pointed above, timely administration of aspirin reduces the mortality in MI significantly. For this purpose only soluble aspirin which dissolves immediately has to be given so that it can be absorbed rapidly. In contrast, if enteric coated aspirin is used it might take minimum 3-4 hours for absorption and to reach effective concentration in plasma[5,6]. Hence, the practicing family physicians should be aware of the differences in the absorption of these two preparations of aspirin and prescribe accordingly.

It is good to note that 90.47% of practicing physicians are familiar with the ECG finding of MI, as ECG is the most effective, simple, and cost effective investigation for guiding on the line of management of suspected chest pain.

On analyzing the advice given by practicing physicians at the time of referral, 47.61% preferred immediate referral to higher centre. While 9.52% opined that tab. Aspirin should be given pre hospitably, reassurance to the patient as a psychological support was insisted by 14.28% of physicians only. Needless to say that the psychological support to patients who are under high stress will definitely improve the prognosis and the family physicians should be made to realize the importance of psychological support in time of crisis.

Reperfusion therapy in the form of primary percutaneous coronary intervention (PPCI) has become the gold standard for treatment of acute MI [7]. As "Time is Myocardium" in the management of MI, timely referral to appropriate centre is eminent. Further, PPCI performed within 3 hours gives excellent results and PPCI performed after

3 hours has not yielded gratifying results. PPCI performed after 12 hours is of doubtful value. In the present survey, only 33.33% of the family physicians favored PPCI; thrombolysis with streptokinase was considered as the latest treatment by 28.57%. Only one primary care physician was of the opinion that patient to be referred to a corporate hospital with excellent facilities for cardiac surgery, irrespective of distance.

The suggested guideline in country like India on the management of MI is as follows: where facilities available to transport the patient within 3 hours to catheterization laboratory, patient should be referred for PPCI. If no such facilitates are available, immediate thrombolysis with tenecteplase should be preferred modality of treatment now. Streptokinase is widely used now in India for thrombolytic therapy; however occluded infarct related arteries had opened in 31% of patients only who were treated with streptokinase, where as the percentage was 62% in case of tenecteplase[8]. Further tenecteplase was found to be more efficacious than streptokinase in preventing cardiogenic shock which is a serious complication of MI[9]. On the other hand, one vial of tenecteplase costs around Rs 30,000 in contrast to streptokinase which costs around Rs 2,500 only. However MI is a killer disease and when life is lost by MI, it is not the loss of single individual but the whole family suffers especially when the victim is the bread winner of the family. Hence on considering the family as a whole there should be no hesitation to use tenecteplase especially when facilities for PPCI are not available. In the present study only 34.52% of the physicians felt that tenecteplase should be the latest treatment.

In the management of MI, the family physicians should be aware of the fact that patient should be referred within 3 hours of the attack of MI to a nearby cardiac centre with catheterization laboratory facilities and not to a corporate hospital with all modern facilities but situated some 300 to 400kms away which takes about not less than 5 to 6 hours of travel to reach the hospital. It is good to note that except one family physician all others in the study were thinking on these lines.

It is estimated that PPCI is available in <25% of hospitals even in USA[10]. These facilities may be available in < 10% of hospitals in India. Under these circumstances it appears that in India thrombolytic treatment despite its short coming is the preferred initial therapy.

The thrombolytic agents available are streptokinase and recombinant tissue-type plasminogen activator (rtPA) such as alteplase and tenectaplase. As already mentioned, compared to other thrombolytic agents streptokinase is least costly (approximately Rs 2,500) but clot dissolution occurs more promptly with tenecteplase and alteplase[11]. Further it has lower incidence of bleeding and mortality rate compared to streptokinase[12]. The cost of tenecteplase is around Rs 30,000. On the contrary, the cost of alteplase is around Rs 90,000. Alteplase and streptokinase must be given through continuous IV infusion for 90 minutes and 60 minutes respectively which need supervision by an experienced physician, where as tenecteplase is given as 5 second IV bolus[13]. Tenecteplase has even been suggested as a pre-hospital thrombolytic agent by primary health care physicians[14]. The present survey revealed that only 34.52% of physicians are aware about the use of tenecteplase for immediate thrombolysis and its ease of administration.

With regard to maximum period of time to refer to a catheterization laboratory, 58.33% of physicians opted within three hours, 29.76% opted within 6 hours, and 9.52% opted within 12 hours. Only one physician was on the opinion that 24 hours is maximum time. Now it is well established that patients with MI should have PPCI within 90 minutes of arrival to the hospital to get maximum benefit[15]. Further timely reperfusion therapy has shown that long-term mortality rate in patients with MI is 15.4% when reperfusion therapy is started within 60 minutes and this mortality doubles to a rate of 30.8% when the reperfusion therapy is started after more than 180 minutes[16]. Hence, we feel that training programs may be arranged for family physicians focussing the value of time in management of MI.

It is worth mention here that the first author of this article, while working as duty physician in intensive coronary care unit of government hospital, one patient with MI was brought by his wife. She requested with tears to save life of her husband as she just came from a private hospital where she was asked to pay Rs 30,000 for an injection which has to be given immediately to save the life of her husband. Unable to pay the money immediately, the hospital doctors advised her to take her husband to a government hospital and she brought her husband here. We cannot find fault with private hospitals for their strict behavior as apart from doing service, they have to survive as well. With a heavy heart it is to note that most of government hospitals do not have a stock of tenecteplase but only streptokinase is available as an inferior alternative to tenecteplase. Under the current treatment scenario, we strongly suggest that tenecteplase should be kept stocked in all government general hospitals not minding the cost, on considering that loss of one life will be suffering to entire family and when the family suffers it is ultimately a suffering and burden to the nation.

Conclusion

Family practitioners play a major role in early management of acute MI. Most of the patients consult the family physicians first since they usually know them well. The family physicians should be able to suspect acute MI and diagnose from ECG and initiate early treatment/ referral, so that lives of many patients may be saved. Proper advice and correct timely directions certainly can reduce the mortality and morbidity in MI. Our present survey revealed that though the family physicians are well versed with the ECG, an important investigation, awareness program pertaining to use of analgesics, referral time to PPCI, use of correct thrombolytic- as a whole on the current strategies of management of MI be organized. Professional bodies like Indian Medical Association, Association of family physicians, Government general hospitals and corporate cardiac centers can play a major role in updating the knowledge of family physicians by arranging continuing medical education and refresher courses, which is the need of the hour.

References

1 Gupta R — Recent trends in coronary heart disease epidemiology in India. *Indian Heart J* 2008; **60:** B4-18.

2 Nallamothu BK, Bradley EH, Krumholz HM — Time to treatment in Primary coronary intervention. *N Engl J Med* 2007; **357:** 1631-8. http://www.nejm.org/doi/pdf/10.1056/NEJMra065985.

3 Yuxiang Dai, Junbo Ge — Clinical use of aspirin in treatment and prevention of cardiovascular disease. Thrombosis. Volume 2012, ID 245037. Doi:10.1155/2012/245037.

4 Vergnion M, Degesves S, Garcet L, Magotteaux V — Tramadol, an alternative to morphine for treating posttraumatic pain in the prehospital situation. *Anesth Analg* 2001; **92:** 1543-6.

5 Muir N, Nichols D, Clifford JM, Stillings MR, Hoare RC — The influence of dosage form on aspirin kinetics: implications for acute cardiovascular use. Current medical research and opinion. *Informa healthcare* 1997; **13:** 547-53.

6 Cox D, Maree AO, Dooley M — Effect of enteric coating on antiplatelet activity of low-dose aspirin in healthy volunteers. *Stroke* 2006; **37:** 2153-2158. DOI: 10.1161/01.STR.0000231683.43347.ec

7 Nordt T K, Bode C — Thrombolysis: newer thrombolytic agents and their role in clinical medicine. *Heart* 2003; **89:** 1358-62.

8 Chesebro JH, Knatterud G, Robberts R, Borer J, Cohen LS, Dalen J, *et al* — Thrombolysis in Myocardial Infarction (TIMI), Phase I: A comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. *Circulation* 1987; **76:** 142-154. Doi: 10.1161/01.CIR.76.1.142

9 Otall PS, Talwar KK — Limitation of currently available thrombolytic therapy. Indian heart journal. 2009, sep- oct: 470-475.

10 Mun K. Hong. Recent advances in the treatment of ST-Segment elevation myocardial infarction. Scientifica. Hindawi Publishing Corporation. 2012. ID 6836683. http://dx.doi.org/10.6064/2012/683683

11 Alward P — Acute myocardial infarction: early treatment. *Aust prescr* 1996; **19:** 52-54.

12 Trujillo E, Bellido I, Pablo JD, Garcia Arnes JA — Alteplase was more efficient than streptokinase, reteplase and tenecteplase in elevated-ST-segment acute myocardial infarction treatment. Proceedings of british pharmacological society. pA2 online E-journal of british pharmacological society. 2012 .Volume10. Issue 3. Abst395P. http://www.pa2online.org/abstract/abstract.jsp?abid=30493

13 Tanswell P, Modi N, Combs D, Danays T — Pharmacokinetics and Pharmacodynamics of tenecteplase in fibrinolytic therapy of acute myocardial infarction. *Clinical pharmacokinetics* 2002; **41:** 1229-45. http://link.springer.com/article/10.2165/00003088-200241150-00001.

14 Saran RK, Sethi R, Nagori M — Tenecteplase- The best among the equals. *Indian Heart J* 2009; **61:** 4454-8.

15 Antman E, Hand M, Armstrong PW — 2007 focused update of the ACC/AHA 2004 guidelines for the management of patient with ST-Elevation myocardial infarction: A report of the American college of cardiology/ American heart association task force on practice guidelines. *J Am Coll Cardiol* 2008, **51:** 210-47.

16 Terkelsen CJ, Sorensen JT, Maeng M, Jensen Lo, Tilsted HH, Trautner S, *et al* — System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. *JAMA* 2010; **304:** 763-71.

Observational Study

Anti D injection to Rh negative mothers – a relook

Barunoday Chakraborty[1], Sibapada Mondal[2]

Presence of fetal cells in maternal blood was demonstrated by application of Acid elution wayback in 1957. Woodrow and Finn first produced evidences that transplacental haemorrhage (TPH) occurs during labour, at term and at sensitizing events e.g miscarriage, antepartum haemorrhage, amniocentesis. Maternal alloantibodies (IgG) develop against the RhD positive fetal cells which cross the placenta and destroys the fetal red cells thus causing haemolytic disease of fetus and newborn(HDF/N). Routine post natal administration of anti D immunoglobulin (IgG) to the Mother who has delivered a Rh positive neonate has reduced incidence of alloimmunisation from 16% to 2%; and a further decrease in incidence to 0.07% was observed when Inj. Anti D prophylaxis was given to all Rh- Mothers at 28 weeks and again after delivery should the Neonate is Rh positive. Studies say that a dosage of 300 micrograms (1500 IU) Anti D immuglobulin can neutralize 15 ml of fetal red cells or 30 ml of fetal blood and by this principle when the fetomaternal haemorrhage (FMH) volume is larger than 30 ml an additional dosage of anti D would be required. Accordingly different countries have developed their own protocol of appropriate doses of anti D injection. In our institution we administer 300ug of anti D igG to all Rh negative mothers who has delivered an Rh positive baby within 72 hours of birth. The same procedure is followed after a miscarriage also. But a number of literature has shown that only 0.4% woman have a TPH of more than 15 ml and therefore it is logical to think that in nearly 99% cases a 300µg anti D IgG is excessive and unnecessary and carries not only the burden of huge cost but also an increased risk of parentally transmitted diseases. Hence the present study was undertaken to assess the fetomaternal haemorrhage in cases of normal delivery, caesarean section and miscarriages by kleihauer Betke test (KBT) of maternal blood samples. Fifty cases of normal delivery, 50 cases of caesarean section and 50 cases of late miscarriage were randomly selected and it was found that KBT was negative among 44 to 50 % cases. In majority of cases an FMH of less than 4 ml was seen in 38% after normal delivery, 32% after caesarean section and 38% after late miscarriages. An FMH of 4 to 10 ml occurred in 10% cases of normal delivery and miscarriages and 18% after caesarean sections. Larger volume FMH of 10 to 30 ml was seen only in 2 to 4% of cases and FMH of more than 30 ml was rare. So this study indicated that in nearly 84% cases a dose of 500 IU (100 µg) anti D IgG would be sufficient when administered within 72 hours post delivery or caesarean section or miscarriage. A KBT of maternal blood sample would indicate whether a larger fetal bleed has occurred or not. In that case an additional dose of anti D IgG can be calculated and administered on the following day thus saving a considerable cost and also reducing the risk of blood borne diseases.

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Key words **: HDF/N, Anti D IgG, FMH, KBT.**

In 1966 J. C. WOODROW and R. FINN first produced evidence that fetal cells are not uncommon in maternal blood after delivery and that in majority of cases Transplacental haemorrhage (TPH) occurs during labour, often when it was a complicated one. They also said that there occurs progressive increase in the incidence of fetomaternal haemorrhage (FMH) as the pregnancy approaches term[16]. Maternal alloantibodies (IgG) develop against the Rh D positive fetal red cells due to high immunogenicity of D antigen. Alloimmune haemolytic diseases of the fetus and newborns (HDF/N) results from the destruction of fetal red cells by maternal Immunoglobulin (IgG) antibodies that gain access to the fetal circulation during pregnancy especially later weeks and also at sensitising events (eg threatened miscarriage, incomplete miscarriage, antepartum haemorrhage, trauma, external cephalic version, amniocentesis etc)[1-6] . In 1957 Kleihauer, Betke and Braun first demonstrated the presence of fetal cells in the maternal circulation by application of the acid elution principle to identify fetal erythrocytes[7]. Approximately 16% of Rh D–negative women who deliver a Rh D–positive fetus become alloimmunised if RhIG is not administered in due time in appropriate doses. The routine administration of anti-D immunoglobulin to Rh D negative women within 72 hours of delivery of a Rh D positive infant, has decreased the risk of alloimmunisation to approximately 2%.

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Since the introduction of anti-D immunoglobulin prophylaxis at 28 weeks to all D-negative women and again after delivery, the incidence of anti-D isoimmunisation was reduced from 16% to 0.07%[8-11]. Each 300 µg of anti-D immune globulin can neutralize 15 ml of fetal red blood cells or 30 ml of fetal blood[12]. By this principle, when the FMH volume is larger than 30 ml Rh D positive blood, additional doses of anti- D immunoglobulin would be required.

The possibility to accurately detect FMH and precisely determine its volume would enable us a more effective and less costly method of prevention of RhD alloimmunisation. Anti-D immunoglobulin could be administered only in indicated cases and only in doses logically necessary for prevention of RhD alloimmunisation by neutralising the specific amount of FMH[13].

In United Kingdom Blood Transfusion Services, Immunoglobulin Working Party, 1991, stated that at least 500 IU (100µg) anti-D immunoglobulin must be given to every RhD negative women with no preformed anti-D antibody within 72 hours of delivery of a RhD positive infant. This dose will be sufficient to prevent alloimmunisation from a 4 ml of fetal red cells bleed. Only 0.4% of women have a TPH of more than 4 ml and o.3% of women have a TPH of more than 15 ml and will not be protected with 500 IU (100 µg) ant-D Ig. It is therefore important that the amount of any fetomaternal bleed accurately estimated so that if necessary a supplementary anti-D dose can be administered to prevent maternal alloimmunisation[14]. Contrary to what is done in England in our country we give a flat dose of 1500 IU (300 µg) anti-D Ig to all RhD negative mothers who has delivered a RhD positive infant or after a miscarriage. But, kipping in view of the above fact that only around 0.4% of women have a TPH of more than 15 ml, it is logical to think that a large amount of anti-D that is used in our country is redundant or unnecessary in nearly 99% cases. This excessive amount of anti-D carries not only a burden of huge cost but also there is an increased risk of parenterally transmitted diseases like HIV, Hepatitis, Creutzfeldt-jakob disease. Hence the logical thinking is to obviate these risks and to reduce the cost should a rapid and accurate assessment of fetomaternal haemorrhage is done in a laboratory. Therefore the present study is undertaken to assess as far as accurately the amount of fetomaternal haemorrhage caused by a delivery, caesarean section or by a miscarriage by Kleihauer-Betke test of maternal blood sample against a positive control of cord blood diluted in adult blood. In 2013 Cedric Pastoret *et al* after their large study in France opined that correct detection and quantification of FMH is critical for the obstetric management of Rhesus D (RhD) negative women. The amount of fetal red cells (RBCs) in the maternal circulation determines the therapeutic dose of anti-D Ig necessary to prevent alloimmunisation[15].

Rhesus (Rh) D immunoglobulin (anti-D) is a human blood product prepared from plasma obtained from a small group of immunised volunteer donors. It has to be used since the 1960s in women who are RhD negative to prevent RhD alloimmunisation after giving birth to a baby who is RhD positive. Prevention of RhD alloimmunisation has been a major medical achievement, as RhD immunisation is a significant cause of perinatal mortality and morbidity in subsequent pregnancies of affected women. The Kleihauer-betke test (KBT) is the most widely used approach of FMH detection. The test is based on the visual microscopic counting of fetal RBCs on a maternal blood film. In acid condition fetal and adult haemoglobin have differences in solubility properties. Haemoglobin F (HbF) resists to acid elution and fetal RBCs are stained in bright pink, while haemoglobin is eluded from adult RBCs that appear as Ghost cells. The lack of precision is in part due to subjective identification of adult cells with increased content of HbF, also called F cells, physiologically increased during pregnancy[16-17]. Automated detection of fetal cells on blood films stained with KB method was reported to be more precise than KBT decreasing specially the inter-observer variation[18]. Flow cytometry (FCM) is a candidate method of FMH quantification. Indeed FCM assays exhibit a better reproducibility and a more reliable quantification of fetal RBCs than KBT[19]. It could not distinguish fetal RBCs from adult cells in case of RhD immunocompatibility. Latter FCM used monoclonal anti HbF antibody that allowed discrimination of three distinct populations of fetal RBCs, F cells and adult RBCs. The quantification of F cells provided by FCM eliminated a major drawback of KBT. In this context "FMH QuikQuant" become a new CE marked kit (Conformite Europeene), which included a monoclonal HbF antibody and propidium iodide as a specific marker of nucleated cells[20,21]. The analysis of artificial mixtures containing 1-100 fetal RBCs per 10000 adult RBCs together with the investigation of pregnant women samples allowed the author to validate that "FCM QuikQuant kit" to be a reliable and efficient method to screen FMH[22] (Table 1).

Administration of 100 IU (20 µg) anti-D Ig has been demonstrated to protect against 1 ml of fetal red cells, 500 IU (100µg) should protect against FMH of up to 5 ml of fetal red cells and 1500 IU (300 µg) anti-D Ig against FMH of approximate 15 ml of fetal red cells[23]. Before 20 weeks of gestation 250 IU should be given. After 20 weeks gestation blood should be taken at least for the conventional KBT to estimate the size of FMH and 500 IU of anti-D IgG should be given[24]. **There are differences internationally in the approach to post-partum anti-D prophylaxis not only in the dose of anti-D used but also in whether testing is perform to quantitate the volume of FMH.** In Australia, UK and the United States post-partum

anti-D doses of 600 IU (120 µg), 500 IU (100 µg), 1500 IU (300 µg) respectively are administered to RhD negative women. These doses are sufficient to cover RhD positive fetal RBCs bleeds of 6ml, 5ml and 15 ml respectively. The FMH volume then quantitated and additional anti-D Ig is given if necessary. In other countries (such as Germany and other European countries) a large dose of anti-D (1500 IU) is given. But FMH volume is not quantitated[25,26,27].

Materials and Methods

We have randomly selected 150 mothers admitted to our Department (Obstetrics and Gynaecology B.S Medical College Bankura) of whom 50 cases were after their normal delivery, 50 after caesarean section and 50 were cases of late 1st trimester miscarriage (>10 weeks) & second trimester miscarriages. Cases with early miscarriages, Molar pregnancies, and complicated pregnancy conditions eg Abruptio placenta, pre-eclampsia, preterm or pre labour rupture membrane, multiple pregnancy were excluded.

Feto-maternal haemorrhage was estimated in all cases by using the Kleihauer-betke test (KBT) and the following formula :

FMH (ml of fetal RBC) = No. of fetal cells counted / No. of maternal cells counted X 1800 X 122/100 X 100/92[24].
or, Can be simplified to:

$$\frac{\text{Number of fetal cells per high power field}}{\text{Number of maternal cells per high power field}} \times 2400 \text{ ml packed fetal red cells.}$$

For example, if the number of fetal cells is 9 and maternal cells 2000, then the fetal bleed will be calculated to be:

$$\frac{9 \times 2400}{2000} = 10.8 \text{ ml packed fetal red cells}^{24}.$$

Study Technique :

Patients were selected randomly. 50 cases of normal delivery, 50 cases of caesarean section and 50 cases of miscarriage were included in the study. Feto-maternal haemorrhage was estimated by using the kleihauer-betke test (KBT). Maternal blood was collected within 24 hours of delivery, miscarriage and caesarean section in an EDTA vial. 3 drops of 0.85% saline was mixed with 2 drops of EDTA blood in the test tube. From one drop of this diluted blood film was drawn on a glass slides. Immediately after drying the film it was put in 80% ethanol in a Coplin jar for 5 minutes. Then the slides were rinsed rapidly in tap water and were kept vertically on a bloating paper for about 10 minutes to get dried. Next the slides were placed in a Coplin jar containing the Elution solution (0.1% erythrosine) for 20 seconds. Then the slides were washed thoroughly in water and finally were placed in the counterstaining solution (1% Eosin) for 2 minutes. Then they were rinsed in tap water and were dried in the air at room temperature. Films prepared from a fresh EDTA cord blood added to 100 times adult whole blood to give a dilution of 1:100 to develop a positive control. Blood film was drawn from normal adult male in the same way so as to provide a negative control. Fetal cells were stained red and adult ghost cells were stained pale pink. Screening of the slides (and positive control) was done by viewing under low power microscope using x10 objective. At least 25 low power fields were screened. If the screening shows fetal cells then fetal erythrocytes were counted in 2000 background maternal red cells under high power field x40 objective where there were at least 100 adult cells present in this high power field. An area of the film was selected where cells were touching but not overlapping.

Table 1 — *Quantification of FMH (Categorized) by KBT*

Procedure	Amount of FMH	No of Cases	Percentage
Normal Delivery (n=50) :			
	Negative	24	48%
	< 4 ml	19	38%
	4-10 ml	5	10%
	10-30 ml	2	4%
	>30 ml	0	0
	Total	50	100%
Caesarean Section (n=50) :			
	Negative	22	44%
	<4 ml	16	32%
	4-10 ml	9	18%
	10-30 ml	2	4%
	>30 ml	1	2%
	Total	50	100%
Miscarriage (n=50) :			
	Negative	25	50%
	<4 ml	19	38%
	4-10 ml	5	10%
	10-30 ml	1	2%
	>30 ml	0	0
	Total	50	100%

Observation and Discussion

The dye we have used for staining the slides is 88% Erythrosine Supra, manufactured and marketed by German Colorcon India, Gujrat (Fig 2). It's a red colour powder from which 0.1% erythrosine solution was made and used for our study purpose. Here somehow the acid elution of the adult cells has worked poorly. However distinct fetal cells were seen as large pale pink cells with multilobed nuclei sparsely scattered over a field of many small pink adult cells. May be that the acid elution worked poorly because of faulty pH of the solution resulting in failure to have a proper ghosting of the maternal cells. This could not be corrected by us even making repeated preparations. However with practice fetal cells could be identified distinctly. Till date to us the matter remains unresolved. However looking at the negative control slides everyday during examination the morphology of the adult cells was reviewed afresh and compared. Any doubt during examination was alleviated looking at the positive control slides

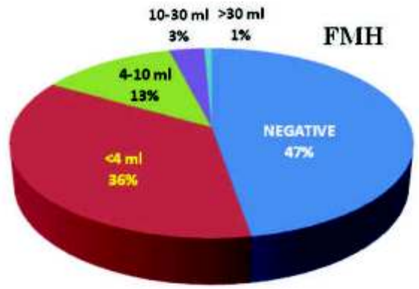

Fig 1

Fig 2

which contain known concentration of fetal cells scattered among the adult cells. And therefore we do agree that there is enough scope of further improvement in the staining process to obviate the interobserver variability. Overall in this study the picture was a negative KBT test, ie absence of fetal cells in the slides was of the order of 48% after normal delivery, 44% after caesarean section and 50% after miscarriage. Majority of the study cases had an FMH < 4 ml in all the three categories; 38% after normal delivery, 32% after caesarean section and 38% after late miscarriage. FMH of 4-10 ml occurred around 10% of cases of normal delivery and miscarriages and 18% after caesarean section. Larger volume FMH of 10-30ml occurred in 2 cases (4%) after normal delivery, 2 cases (4%) after caesarean section and one case (2%) after miscarriage. Only in one case there was a FMH of >30 ml after caesarean section. The details of the case were not known (Fig 1). Augustson *et al* in their study commented that 250 IU (50 µg) dose could be routinely used for 98.5% of RhD negative women post-partum. [25] Urgessa et al in their study concluded that around 92.5% of their study cases by KBT method and 87% by FCM method the calculated FMH volume was < 5ml of fetal RBCs and hence 500 IU (100µg) anti-D Ig would be sufficient in the majority of the RhD negative mothers.[29] This result is also consistent with the study conducted by Lubusky et al where they concluded that for the prevention of RhD alloimmunisation a dose of anti-D Ig 100µg should be sufficient in great majority of cases[28] (Figs 3-5).

So, in conclusion the current study indicates that in the great majority of the cases (84%) a dose of 500 IU (100 µg) of anti-D Ig would be sufficient when administered within 72 hours of post-delivery, post-caesarean or post-abortal. A KBT test of maternal blood samples would indicate whether a larger fetal bleed of more than 4ml has occurred or not. Should it happen additional dose of anti-D can be calculated and administered on the following day of initial dose. Because KBT is an easy, simple and rapid laboratory method, with experience and practice the accuracy of the test would increased day by day. Thus a huge quantity of costly RhD Ig can be saved reducing the burden of the government expenditure to a large extent, because the anti-D is freely provided to the Rh negative mothers in our institution.

References

1 Greer JP, Foerster J, Lukens J, Rodgers G, Paraskevas F, Glader B — Autoimmune Hemolytic Anemia. In Wintrobe's Clinical Hematology. 11th edition. Edited by Neff A. USA: Lippincott Williams & Wilkins Publishers; 2003: 2363-72.
2 AABB — Technical Manual. 15th edition. AABB: Bethesda; 2005.
3 Pourazar A, Homayouni A, Rezaei A, Andalib A, Oreizi F — The Assessment of Feto-Maternal Hemorrhage in an Artificial Model Using Anti-D and Anti-Fetal Hemoglobin Antibody by FCM, Iran. *Biomed J* 2008, **12:** 43-8.
4 Lafferty JD, Raby A, Crawford L, Linkins LA, Richardson H,

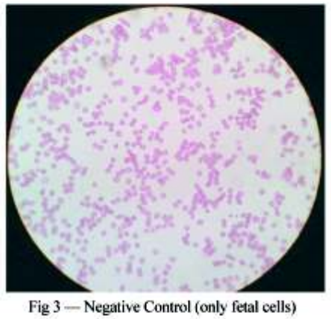

Fig 3 — Negative Control (only fetal cells)

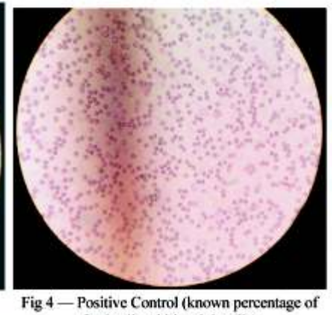

Fig 4 — Positive Control (known percentage of fetal cells within adult cells)

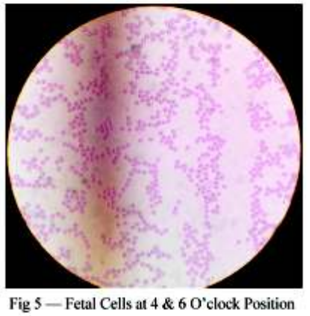

Fig 5 — Fetal Cells at 4 & 6 O'clock Position

Photographs are directly taken from the microscope under x40 objective during the study by a 12mp Canon Digital Camera

Crowther M — Fetal-Maternal Hemorrhage Detection in Ontario. *Am J Clin Pathol* 2003, **119:** 72-7.
5 Blood BCSH — Transfusion and General Haematology Task Forces. The estimation of fetomaternal haemorrhage, GUIDELINES. *Transfus Med* 1999, **9:** 87-92.
6 Quinley E — Immunohematology, principles and practice. 2nd edition. 1998: 14.
7 Bowman JM, Pollock JM, Penston LE — Fetomaternal transplacental hemorrhage during pregnancy and after delivery. *Vox Sang* 1986; **51:** 117-21.
8 Bowman JM — Controversies in Rh prophylaxis: who needs Rh immune globulin and when should it be given? *Am J Obstet Gynecol* 1985; **151:** 289 -94.
9 Stedman CM, Baudin JC, White CA, Cooper ES — Use of the erythrocyte rosette test to screen for excessive fetomaternal hemorrhage in Rh-negative women. *Am J Obstet Gynecol* 1986; **154:** 1363-9.
10 Ness PM, Baldwin ML, Niebyl JR — Clinical high-risk designation dose not predict excess fetal-maternal haemorrhage. *Am J Obstet Gynecol* 1987; **156:** 154-8.
11 Bowman JM, Pollock JM — Antenatal Rh prophylaxis: 28 week gestation service program. *Can Med Assoc J* 1978; **118:** 627-30.
12 Pollack W, Ascari WQ, Kochesky RJ, O Connor RR, Ho TY, Tripodi D — Studies on Rh prophylaxis. I. Relationship between doses of anti-Rh and size of antigenic stimulus. *Transfusion* 1971; **11:** 333-9.
13 Lubusky M — Prevention of RhD alloimmunization in RhD negative women. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2010, **154:** 3-8.
14 Blackwell Science Ltd — Estimation of Fetomaternal Haemorrhage; *Transfusion Medicine* 1999; **9:** 87-92.
15 Cedric Pastoret, Jerome Le Priol, Thierry Fest, and Mikael Roussel — Evaluation of FMH QuikQuant for the Detection and Quantification of Fetomaternal Haemorrhage. *Cytometry Part B (Clinical Cytometry)* 2013; **84B:** 37-43.
16 Woodrow JC, FINN R — Transplacental Haemorrhage. *Brit J Haemat* 1966; **12:** 297-309.
17 Popat N, Wood WG, Weatherall DJ, Turnbull AC — Pattern of maternal F-cell production during pregnancy. *Lancet* 1977; **2:** 377-9.
18 Pelikan DMV, Mesker WE, Scherjon SA, Kanhai HHH, Tanke HJ — Improvement of the Kleihauer–Betke test by automated detection of fetal erythrocytes in maternal blood. *Cytometry Part B Clin Cytom* 2003; **54B:** 1-9.
19 Bromilow IM, Duguid JK — Measurement of feto-maternal haemorrhage: A comparative study of three Kleihauer techniques and two flow cytometry methods. *Clin Lab Haematol* 1997; **19:** 137-42.
20 Igout J, Fretigny M, Vasse M, Callat MP, Silva M, Willemont L, Gelle M, Lenormand B — Evaluation of the coulter LH 750 haematology analyzer compared with flow cytometry as the reference method for WBC, platelet and nucleated RBC count. *Clin Lab Haematol* 2004; **26:** 1-7.
21 Tsuji T, Sakata T, Hamaguchi Y, Wang FS, Houwen B — New rapid flow cytometric method for the enumeration of nucleated red blood cells. *Cytometry* 1999; **37:** 291-301.
22 Cedric Pastoret, Jerome Le Priol, Thierry Fest, Mikael Roussel — Evaluation of FMH QuikQuant for the Detection and Quantification of Fetomaternal Haemorrhage; *Cytometry Part B (Clinical Cytometry)* 2013; **84B:** 37-43.
23 National Health and Medical Research Council: Guidelines on the prophylactic use of Rh D immunoglobulin (anti-D) in obstetrics. Australia: *National Blood Authority*; 2003: 1-36.
24 Austin E, Bates S, Silva M, Howarth D, Lubenko A, Rowley M, Scott M, Thomas E, White J, Williams M — BCSH Blood Transfusion and General Haematology Task Forces. The estimation of fetomaternal haemorrhage, *Guidelines* 2009, 1-23.
25 Bradley M Augustson, Elizabeth A Fong, Dianne E Grey, Janine I Davies, Wendy N Erber – Postpartum anti-D: can we safely reduce the dose? ; *MJA* 2006; **184**:12;awery67890 611–613/ a 5
26 Royal College of Obstetricians and Gynaecologists. Clinical green top guidelines. Use of anti- D immunoglobulin for Rh prophylaxis (22) — revised May 2002. Available at: http://www.rcog.org.uk/index.asp?PageID=512 (accessed May 2006).
27 National Blood Authority. Guidelines on the prophylactic use of Rh D immunoglobulin (anti- D) in obstetrics — June 2003. Canberra: NBA, 2003. Available at: http://www.nba.gov.au/pubs.htm (accessed May 2006).
28 Lubusky M, Simetka O, Studnickova M, Prochazka M, Ordeltova M, Vomackova K — Fetomaternal hemorrhage in normal vaginal delivery and in delivery by cesarean section. *Transfusion* 2012, **52:** 1977-82.
29 Fekadu Urgessa, Aster Tsegaye — Yirgu Gebrehiwot and Asaye Birhanu; Assessment of feto-maternal hemorrhage among rhesus D negative pregnant mothers using the kleihauer-betke test (KBT) and flow cytometry (FCM) in Addis Ababa, Ethiopia. *BMC Pregnancy and Childbirth* 2014, **14:** 358.

Observational Study

Intraoperative difficulties and challenges in 261 repeat caesarean section — a rural hospital experience in Pondicherry

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The objective of the study is to analyse intraoperative difficulties encountered and challenges faced in repeat C sections. Retrospective analysis was done on medical records from 2008-2010, on 261 repeat caesarian sections done in SMVMCH, a rural referral hospital. Incidence of primary section in our study is 43.96 % and repeat section 21.85%. Referral 55.6%. Previous one section women were 70%. All had non closure of parietal peritoneum and one layer closure of uterus during previous section. There was difficulty in entering the peritoneal cavity in 136 (52.1%) women due to adhesions in 63, ventrofixation of uterus to abdominal wall 24, and cicaterised RPM scar in 49. Lower segment was inaccessible in 79 (32.6%) due to adherent bladder 37, adherent rectus muscle 6, dense adhesions in 36. Six women needed classical section, bladder injury repair 9, rent repair of dehiscent scar 41 (15.77%). Four had caesarean hysterectomy (1.05%). Relaparotomy was done for intractable intra abdominal bleeding needing uterine artery ligation in 2 post caesarean women and internal iliac artery ligation in one post caesarean hysterectomy vault bleeding. We did not have any mortality.

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Key words **: Repeat cesarean section adhesion bladderinjury hysterectomy.**

Rate of cesarean section has increased due to cesarean delivery on maternal request (CDMR) and newer indications. 68.5% were unbooked, 55.6% were referrals from health centres and 22.3% by practioners. Changing trends in techniques[4,5], like non closure of parietal peritoneum[4] has threefold increase in the formation of dense adhesions. Scar dehiscence and adherent bladder was more in uterine closure with one layer[5,6]. Difficulty in entering lower segment was due to dense adhesions, adherent bladder and rectus muscle[4,5] over the scar, which increase surgery time and difficulty in delivering the baby[1,6]. Caesarean hysterectomy, uterine artery ligation and internal iliac artery ligation are life saving procedures. Decision to reopen in intractable intra abdominal bleeding following caesarean and preservation of uterus in young women with atonic PPH uterine rupture are dilemmas faced.

Objective : To analyse intraoperative difficulties encountered and challenges faced in repeat C sections.

Material and Methods

The medical records of 261 repeat C sections done in SMVMCH, a teaching hospital and teritiary referral centre were selected for the study. Medical records were analysed retrospectively to find out the difficulties encounted and challenges faced during repeat sections and management of intraoperative complications.

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Observation

Total no. of deliveries between 2008-2010 were 1194. Primary cesarean section 525 and repeat cesarean section 261. Incidence of primary sections was 43.96%. Rate of C.sections is increasing due to increased fetal causes and cesarean delivery on maternal request (CDMR). Incidence of repeat section is 21.85%. Women in the age group of 21-25 were 68.2% and 70% were previous one section women. Elective section were 44.4% and emergency 55.6%. Skin incision was RPM in 100 and suprapubic transverse in 161. Uterine incision was low transverse in 255 and upper midline in 6. More than one complication was noted in 102 women and none in 89. All 261 repeat section women had non-closure of parietal and visceral peritoneum, one layer closure of uterus during previous section.

Non-closure of parietal and visceral peritoneum lead to adhesion on anterior abdominal wall, rectus muscle and bladder. There was difficulty in entering peritoneal cavity in 44.5% women, (Table 1) due to adhesions. Single layer closure of uterus of cause dense adhesions, adherent bladder and rectus muscle over the scar, causing difficulty in reaching the lower segment (Table 2). Difficulty in delivering the baby and more bleeding was seen during elective caesarean section due to thick lower segment.

Intraoperative complication is shown in Table 3. Extension of the wound, scar dehiscence and PPH were common complications. In 6 women had to undergo classical section due to unapproachable lower segment. In 9 had bladder injury and repair. Four (1.05%) needed caesarean hysterectomy, 3 were admitted in labour and one was planned repeat caesarean section. Hysterectomy was done for scar dehiscence with broad ligament haematoma, complete rupture uterus, uterine sepsis with DIC and vault bleeding with morbid adherent placenta.

Table 1 — *Difficulties in Entering peritoneal cavity*

Factors		No of cases
Cicatrized puckered RPM scar		49
Ventrifixation of uterus on RPM Scar		24
Adhesions –	Flimsy	27
	Dense	36

Table 2 — *Inaccessible lower segment (n=79)*

Factors	No of cases
Dense adhesions	36
Adherent bladder	37
Adherent rectus muscle	6

Table 3 — *Intra operative complications*

Factors		No. of cases
Scar dehiscence		41
Extension of uterine scar with Broad ligament hematoma		14
Bladder injury		9
Uterine rupture		5
PPH	Atonic 79 / Traumatic 5	84

Relaparotomy (Table 4) was done in 3 women for intractable intraabdominal bleeding. In 2 post cesarean women Uterine artery ligation was done. Internal iliac artery ligation was done in 1 post cesarean hysterectomy women.

Results

Intraoperative Findings n = 261 repeat Cesarean section

• More Than One Complication, n = 102

Discussion

Incidence of primary caesarean section in our study is 43.96% similar to other authors[1-3,5,8,9]. Rate of caesarean is increasing due to more fetal causes and caesarean delivery on maternal request[1]. Incidence of repeat section in our study is 21.85%, 23.14% in Mahale's[3] and 27.9% in Jitish[5]. In Parveen's[8] study emergency referrals were 60% and ours (55.6%). 70% of our women had one previous caesarean section where as in Praveen's[8] series 57% were previous three caesarean section women. Like Mahale[3] we had 44.4% elective repeat section and 55.6% emergency section. Pratap *et al*[4] has reported noncloure of parietal and visceral peritoneum lead to dense adhesions on anterior abdominal wall, rectus muscle and adherent bladder. We had 37 women with adherent bladder and 9 had bladder injuries[4]. Entering the peritoneal cavity was difficult in 136 women due to cicatersation of RPM scar in 49,[1,3] and ventrofixation of anterior abdominal wall in 24,[2,3]. Dense adhesions in 36,[1,3] and adherent rectus muscle in 6,[4].

Table 4 — *Relaparotomy in intrabdominal bleeding (n=3)*

Procedure	Indication	No. of cases
Uterine artery ligation	Post caesarean Broad ligament hematoma	2
Internal iliac artery ligation	Post caesarian Hysterectomy Vault bleeding	1

Single layer closure of uterus caused dense adhesion[4,5] adherent bladder[4-6] bladder injury[1,4,6] and adherent rectus muscle over the scar[4,6] causing difficulty to approach the lower segment. In our study, we had difficulty in 32.6% (79) women to reach lower segment increasing surgery time. Difficulty in delivering the baby and more bleeding was encountered in 19 women due to thick lower segment in elective caesarean section[1-3,6]. Extension of the uterine scar with broad ligament haematoma was seen in 14 women while delivering the baby[3,10]. Scar dehiscence was seen in 41 women (15.77%) needing rent closure[10]. Five women had rupture uterus[10] (1.05%) PPH was seen in 84 women in our study (32.1%) in Parveen[8] study, 10% and Archana[10] 8%. Caesarean hysterectomy was done in 4 women in our series. Which is comparable with authors[8-10]. Relaparotomy for intra abdominal bleeding was reported by authors[1,8,10]. We had three relaparotomies. In 2 post cesarean women had uterine artery ligation and one post hysterectomy women had internal iliac artery ligation for vault bleeding. Archana[10] has reported one relaparotomy and uterine artery ligation and Praveen8 one internal iliac artery ligation. Arachana *et al*[10] has reported 6 maternal deaths and VVF in their series. We did not have any mortality or VVF in our series. Average hospital stay was 10 days.

Conclusion

Rate of caesarean repeat section is increasing due to more fetal causes[1,2] and caesarean delivery on maternal demand[1] (CDMD). Non closure of visceral and parietal peritoneum[4] and one layer closure of uterus[3,4] cause difficulty in entering peritoneal cavity reaching the lower segment and difficulty in delivering the baby due to formation of adhesions. Repair of bladder, bowel, uterine injury, life saving procedures like internal iliac artery and uterine artery ligation, caesarean hysterectomy are challenges faced when blood and trained personals are not available. Decision to reopen for intractable intra abdominal bleeding following caesarean section, decision to preserve uterus in atonic PPH and uterine rupture in young women are dilemmas faced. High caesarean rate, high morbidity and risk of mortality[1] as often patients report in last moment with labour pain[10].

References

1 Seth Shirish. Kurush P — History of Cesarean Section. *J Obstetric Gynecol India* 2009; **59:** 413-23.

(Continued on page 26)

Observational Study

Analysis of prevalence, risk factors & co-morbid associations between non alcoholic fatty liver disease and type 2 diabetes mellitus in a tertiary care hospital of Eastern India

Manab Nandy[1], Satyaki Chakraborty[2], Asish Kumar Basu[3]

Non Alcoholic Fatty Liver Disease (NAFLD) is one of the commonest causes of elevated liver enzymes in India nowadays. It is well documented that NAFLD prevalence is higher among patients with features of insulin resistance, obesity and dyslipidaemia. This association can promt one to consider NAFLD as a hepatic manifestation of Metabolic Syndrome. On the other hand India is now viewed as one of the largest home of Diabetes in the world . To analyse the close association between Type 2 Diabetes Mellitus (DM) and NAFLD a total of 100 patients were selected in this cross sectional, observational study. This study found significant link between obesity, dyslipidemia, diabetes, and NAFLD, thus establishing some modifiable risk factors and clinical parameters, which should be focused for management by clinicians early during the course of the disease. Significant data for proving an association between the complications of diabetes and NAFLD would highlight a subgroup of Type 2 DM patients requiring earlier intensive therapy and management of risk factors.

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***Key words* : Non alcoholic fatty liver disease, Diabetes mellitus, Co-morbid associations**

NAFLD refers to the broad range of liver pathology ranging from mild steatosis to non-alcoholic steatohepatitis (NASH) in the absence of significant alcohol consumption. Today it is the fourth most common indication for liver transplantation and is one of the commonest causes for elevation of liver enzymes[1,2]. Prevalence of the NAFLD is estimated to be around 9-32% in the general Indian population, with a higher incidence rate amongst obese and diabetic patients[3]. It is well documented that NAFLD prevalence is higher among patients with features of insulin resistance, obesity and dyslipidaemia. This association can prompt one to consider NAFLD as a hepatic manifestation of Metabolic Syndrome[3].

In contrast, Diabetes has been well documented enough for the general population to be aware of its consequences[4]. China and India lead the world with the largest number of diabetes subjects[5]. The threat of end organ complications, nephropathy, retinopathy and neuropathy looms large over the population of uncontrolled diabetics. Furthermore, 15-25% of patients with NAFLD, progress to cirrhosis and its complications over 10-20 years[5].

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Due to the close association between Type 2 DM and NAFLD, the analysis of risk factors is of utmost importance in identifying individuals susceptible to the co-morbid complications arising from either disease. Significant data for proving an association between the complications of diabetes and NAFLD would highlight a subgroup of Type 2 DM patients requiring earlier intensive therapy and management of risk factors.

Aims and Objectives

The aim of this study is to assess the risk factors associated with development of NAFLD in the diabetic study population. It will also aim to identify any co-relation between NAFLD and end organ changes associated with Diabetes such as nephropathy, neuropathy and retinopathy.

Materials and Methods

A total of 100 patients participated in this cross sectional, observational study. After obtaining a certificate of approval from the Institutional Ethics Committee, Patients with Type 2 DM from the Internal Medicine ward of a Tertiary Medical College of Eastern India, were identified by review of their records. The sample population was chosen on the basis of simple random sampling. Each subject was given an 'Informed Consent' along with an 'Information Sheet', specifying the procedures undertaken in this project, in the language of their choice. The choice

of subjects however was dependent on the following criteria:

Inclusion Criteria : Patients having history of Type 2 DM or suffering directly from its complications.

Exclusion Criteria : Patients suffering from Type 1 DM or Maturity Onset Diabetes of Young (MODY) or any form of Secondary Diabetes, Gestational DM, Patients who are on medication that include steroids or drugs that are known to cause fatty liver such as amiodarone, aspirin, methotrexate, anti-viral drugs (nucleoside analogs), tamoxifen, etc.

Patients consuming alcohol greater than 20 ml/day (or >21 drinks per week) and women consuming alcohol greater than 15 ml/day (or >14 drinks per week) as this automatically excludes diagnosis for NAFLD[4].

After sample selection, a screening procedure was implemented to sort the patients into two groups, A and B. The screening was based on evidence of fatty liver on hepatic ultrasonography. The diabetics not showing evidence of steatosis on ultrasonography were grouped in A, and those showing evidence of the same were grouped in B.

Patients in either group were subjected to laboratory Investigations like Liver function tests, HbA1c, urine albumin and creatinine, and lipid profile.

All of the above data was 'cross tabulated' using Microsoft Excel. Data on subjects of either group was tabulated on separate Excel sheets.

The data after cross tabulation was analyzed using 'SPSS version 22'. A logistic regression model was developed to evaluate predictors of NAFLD. Differences between normally distributed variables were assessed using 'unpaired t test'. Categorical variables were assessed using Chi-Square (χ^2) test. Relative Risk (RR) and Odds Ratios (OR) were calculated for hypothesized risk factors. Assuming a confidence interval of 95%, a p-value of less than 0.05 was considered significant.

Observations and Results

A total of 100 patients (60 males and 40 females) suffering from Type 2 DM were enrolled in the study. The mean age of the patients was 55.83± 7.81 (mean± SD). Out of this a cohort of 52 patients were identified as having NAFLD based on the findings on hepatic ultrasonography (Table 1).

Participants with NAFLD had greater mean age (59.07±7.57 years), duration of diabetes (6.48±1.74) and body mass index (27.53±3.05). This particular cohort of patients had higher levels of HbA1c (7.50±1.12), ALT (56.09±13), AST (54.40±6.20) and triglycerides (205.42±34.90). The prevalence of NAFLD was found to be greater in males than females. This is illustrated in Fig 1.

Table 1— *Compares the demographical, clinical and laboratory characteristics of patients with NAFLD with those without NAFLD*

Variable N	Without NAFLD 48	WITH NAFLD 52	P-value
Male (%)	28(58.4)	32(61.5)	
Female (%)	20(41.6)	20(38.5)	
Age (years)	53.39±7.39	59.07±7.57	NS
Length of DM(years)	4.93±2.07	6.48±1.74	p<0.05
B.M.I (kg/m2)	24.66±2.54	27.53±3.05	P<0.05
ALT (IU/L)	18.10±8	56.09±13	p<0.05
AST (IU/L)	19.23±6.74	54.40±6.20	P<0.05
HbA1c(%)	6.46±1.16	7.50±1.12	p<0.05
Triglycerides (mg/dl)	132.18±40.69	206.71±92.90	p<0.05
Cholesterol (mg/dl)	188±30.50	210±54.40	NS
LDL (mg/dl)	126.00±26.20	142.43±48	NS
HDL (mg/dl)	45.20±8.10	38.42±10.00	NS

Out of the 52 patients found to have NAFLD, 12(23%) had normal BMI, 24 (46%) were overweight and 16 (31%) were obese as illustrated in Fig 2.

BMI of 30 or more was considered obese.

Dyslipidemia was determined according to triglyceride, cholesterol and HDL/LDL levels and reference values.The findings are illustrated in Fig 3. In 61.5% (32) of the NAFLD subjects had dyslipidemia compared to 39.6% (19) of the non-NAFLD subjects : χ^2 value=9.75; RR= 1.53, OR= 2.44, p=0.03 (p<0.05, 95% CI).

Incidence of microvascular complications in either group was assessed. The findings are illustrated in Figs 4-7.

In 55.7% (29) of the patients having NAFLD were diagnosed to also have diabetic nephropathy (DN) compared to 35% (17) of the subjects without NAFLD: χ^2 value=4.16,

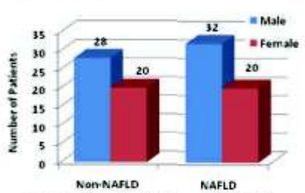

Fig 1— Showing incidence of NAFLD between male and female

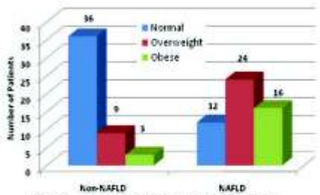

Fig 2 — Showing incidence of NAFLD among overweight and obese patients

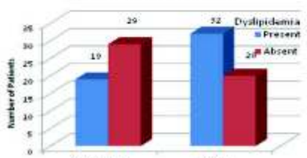

Fig 3 — Comparison of prevalence of dyslipidemia in non-NAFLD and NAFLD group

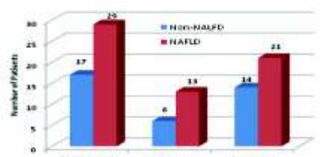

Fig 4 — Incidence of microvascular complications of diabetes mellitus in non-NAFLD and NAFLD group

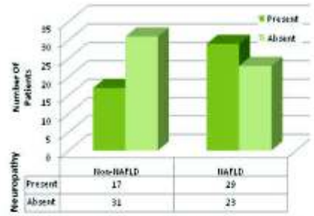

Fig 5 — Comparison of incidence of nephropathy in non-NAFLD and NAFLD group

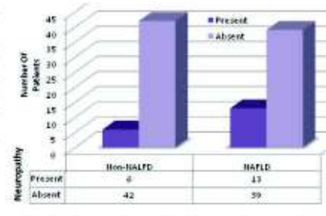

Fig 6 – Comparison of incidence of neuropathy in non-NAFLD and NAFLD group

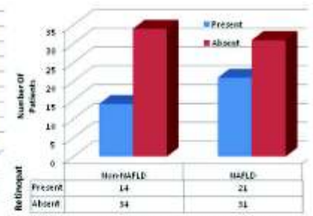

Fig 7 — Comparison of incidence of retinopathy in non-NAFLD and NAFLD group

p=0.041 (p<0.05, 95% CI), OR=2.29, RR= 1.48 (CI= 0.97-2.2).

In 25% (13) of the patients having NAFLD were diagnosed to also have diabetic neuropathy (DPN) compared to 12.5% (6) of the subjects without NAFLD: χ^2 value=2.53, p=0.11 (p>0.05, 95% CI).

In 40.4 % (21)of the patients having NAFLD were diagnosed to also have retinopathy (DR) compared to 29.2% (14) of the subjects without NAFLD: χ^2 value= 1.38, p value= 0.240 (p>0.05, 95% CI).

Discussion

Multiple studies have shown a close association between NAFLD and Type 2 DM. Cusi Kenneth *et al* (2009) pointed out that 60-70% of diabetics show evidence of NAFLD[7]. Sanjay Katra *et al* found the overall prevalence of NAFLD in Type 2 DM patients was to be 56% in Indian population[3]. Gupte P *et al* (2004) and Kamani P *et al* (2007) determined the prevalence to be 12.5% and 20% respectively[8,9]. A number of studies around the world have identified the possible risk factors leading to the development of NAFLD. Type 2 Diabetes Mellitus itself is now considered an independent risk factor for the development of NAFLD[3,4,6].

Study conducted by Hosseinpanah *et al* (2007) found that diabetic patients with NAFLD were more likely to have greater BMI[10].Wen-Shan *et al* (2013) determined the same to be and also came to the conclusion that diabetics with NAFLD have higher levels of liver transaminases as well as lower high density lipoproteins (HDL) level compared to diabetics without NAFLD[11]. This study however used hepatic ultrasonography to detect the presence of steatosis although it has been well established that liver biopsy remains the gold standard for diagnosis of NAFLD[12]. There have been studies linking NAFLD with greater incidences of chronic kidney disease and even identifying NAFLD in the presence of Type 2 Diabetes as a significant cardiometabolic risk factor[13]. In a much more recent study the same author found that diabetic patients suffering from NAFLD had a greater incidence of developing diabetic retinopathy[14].

The prevalence of NAFLD among the diabetic subjects, 52%, is in line with the overall prevalence, 54.5% as postulated by Mohan *et al*[15]. The prevalence of NAFLD in males were greater compared to females, which contraindicates a major pan-Indian study carried out by Kalra *et al* where the researchers had concluded that the female prevalence of NAFLD (60%) was higher than that of males (54.3%)[3].

However the male and female prevalence of 54.3% and 55% respectively is line with many previous studies on co-occurrence of NAFLD and Type 2 DM[9,16].This study revealed that older patients were more likely to develop NAFLD but without statistical significance. Both insulin resistance and obesity are key features of metabolic syndrome and 30% of NAFLD subjects have metabolic syndrome[17].

Greater duration of diabetes and higher HbA1c levels were found to be good predictors of NAFLD prevalence and the presence of microvascular complications. This was similar with the findings by Banerjee *et al* who found that longer duration of diabetes and poor glycemic control were associated with higher rates of progression to a severe form NAFLD, non-alcoholic steatohepatitis (NASH)[18].

This fact is further reinstated by the strong correlation between dyslipidemia, an important predictor of cardiovascular risk, and fatty liver disease. The role of liver enzyme elevation in NAFLD has been widely debated. It has been widely suggested that liver enzyme elevation correlation is related to the degree of steatosis as evidenced on biopsy[8,9,12].

As illustrated in Fig 4, higher rates of microvascular complications were found in the subjects identified as having NAFLD. However, not all the findings were statistically significant. The null hypothesis (H_0) therefore cannot be rejected. The positive correlation of diabetic nephropathy with NAFLD was found to have a p value of 0.041 (p<0.05) however the relative risk of 1.48 lies between a confidence of interval of 0.97-2.20 (includes 1.00 in the reference range), hence eliminating its statistical significance as possible risk factor. Diabetic neuropathy and retinopathy were also found to have a p value of greater than 0.05 and insignificant OR and RR (confidence interval

includes 1.00). The above findings are similar with a study carried out in the Chinese population by Wen Shan et al[11].

Conclusion

This study found significant links between obesity, dyslipidemia, diabetes duration, glycemic control and NAFLD, thus establishing some modifiable risk factors and clinical parameters. Along with medical interventions, these includes dietary modifications and lifestyle changes involving increased exercise. Liver enzyme abnormalities plus Type 2 DM leads to greater risk of cardiovascular and renal disease[13]. Therefore management of NAFLD progression is not just essential for preventing hepatic complications but also important for prevention of cardiovascular disease and renal impairment.

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Conflict of Interest : None declared.

References

1 Angulo P — Nonalcoholic Fatty Liver Disease and Liver Transplantation. *Liver Transpl* 2006; **12:** 523-34.
2 Ruhl CE, Everhart JE — Determinants of the association of overweight with elevated serum alanine aminotransferase activity in the United States. *Gastroenterology* 2003; **124:** 71-9.
3 Kalra S, Vithalani M, Gulati G, Kulkarni CM, Kadam Y, Pallivathukkal J, Das B — Study of Prevalence of Nonalcoholic Fatty Liver Disease (NAFLD) in Type 2 Diabetes Patients in India (SPRINT). *J Assoc Physicians India* 2013; **61:** 448-53.
4 Smyth S Heron — Diabetes and obesity: the twin epidemics. *Nature Medicine* 2002; **12:** 75-80.
5 V Mohan V, Sandeep S, Deepa R, Shah B ,Varghese C — Epidemiology of type 2 diabetes: Indian scenario. *Indian Journal of Medical Research* 2007; 217-30.
6 Hui JM, Kench JG, Chitturi S, Suda A, Farrell GC, Byth K, *et al* — Long term outcomes of cirrhosis in non-alcoholic steatohepatitis compared with hepatitis C. *Hepatology* 2003; **38:** 420-7.
7 Cusi, Kenneth — NAFLD in Type 2 Diabetes Mellitus. *Curr Opin Endocrinol Diabetes Obes* 2009; **16:** 141-9.
8 Gupte P, Amarapurkar D, Agal S, Baijal R, Kulshrestha P, Pramanik S, *et al* — Non-alcoholic steatohepatitis in type 2 diabetes mellitus. *J Gastroenterol Hepatol* 2004; **19:** 854-8.
9 Amarapurkar D1, Kamani P, Patel N, Gupte P, Kumar P, Agal S, *et al* —Prevalence of non-alcoholic fatty liver disease: population based study. *Ann Hepatol* 2007; **6:** 161-3.
10 Hosseinpanah F, Rambod M, Sadeghi L — Predictors of Non-Alcoholic Fatty Liver Disease in Type 2 Diabetes. *Int J Endocrinol Metab* 2007; **2:** 61-9.
11 Wen-Shan Lv, Rui-Xia Sun, Yan-Yan Gao, Jun-Ping Wen, Rong-Fang Pan, Li Li, Jing Wang — NAFLD and Microvascular Complications in Type 2 Diabetes Mellitus. *World J Gastroenterology* 2013; **19:** 3134-42.
12 Saadeh S, Younossi ZM, Remer EM — The Utility of Radiological Imaging in NAFLD. *Gastroenterology* 2002; **123:** 745-50.
13 G Targhar, M Chonchol, G Zoppini, E Bonora — Risk of chronic kidney disease in patients with non-alcoholic fatty liver disease: Is there a link? *Journal of Hepatology* 2011; **54:** 1020-9.
14 G Targhar, G Lippi, L Bertolini, S Rodella — NAFLD is independently associated with increased prevalence of Chronic Kidney Disease proliferative/laser treated retinopathy in Type 2 DM patients. *Diabetologia* 2008; **51:** 444-50.
15 Mohan V, Farooq S, Deepa M, Ravikumar R, Picthumoni CS — Prevalence of non-alcoholic fatty liver disease in urban South Indians in relation to different grades of glucose intolerance and metabolic syndrome. *Diabetes res Clin Pract* 2009; **84:** 84-91.
16 Uchil D, Pipalia D, Chawla M, Patel R, Maniar S, Juneja A — Non-Alcoholic Fatty Liver Diesease(NALFD)- the hepatic component of metabolic syndrome. *J Assoc Physicians India* 2009; **57:** 201-4.
17 Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC — Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology* 2004; **40:** 1387-95.
18 Banerjee S, Ghosh US, Dutta S — Clinicopathological profile of hepatic involvement in type-2 diabetes mellitus and its significance. *J Assoc Physicians India* 2008; **56:** 593-9.
19 Popovic L, Zamaklar M, Lalik K, Vasolic O — Analysis of effect of type 2 diabetes duration on beta cell secretory function and insulin resistance. *Srp Arh Celok Lek* 2006; **134:** 219-23.

(Continued from page 22)

2 Doshi Haresh, Tripathi Jagruti — Cesarean Section – Changing trends – A National Study. *J Obstetric Gynecol India* 2009; **59:** 140-4.
3 Mahale Arun, Ujwala Popaj — Intra operative difficulties in Repeat Cesarean Sections – A study of 287 cases. *J Obstetric Gynecol India* 2008; **58:** 507-10.
4 Bhat Parvati V, Kumar Pratap, Moyya Shrimathi — Should parietal peritoneum be closed at primary Cesarean Section? *J Obstetric Gynecol India* 2009; **59:** 220-3.
5 Shah Jitesh, Mehta Meghana — Analysis of mode of delivery in women with previous one cesarean section. *J Obstetric Gynecol India* 2009 59: 136-9.
6 Blumenfeld YJ, Daniels K — Single versions double layer hysterctomy closure at primary cesarean delivery and bladder adhesions : BJOG – *International Journal of Obstetrics and Gynaecology* 2010; **117:** 690-3.
7 Z shi L Ma Y Yang, H Wang — Adhesion formation after previous cesarean section – meta analysis and systemic review BJOG – *International Journal of Obstetrics and Gynaecology* 2011; **118:** No 4.
8 Marwaha P, Kaur M, Gupta A — Peripartum hysterctomy – A five year study. *J Obstetric Gynecol India* 2008; **6:** 504-6.
9 S Minalini, Jindal M, Kamat A — Obstetric hysterectomy – A life saving emergency. *J Obstetric Gynecol India* 2008; **58:** 138-41.
10 Kumari A, Sahay PB — A clinical review of emergency obstetric hysterectomy. *J Obstetric Gynecol India* 2009; **59:** 424-31.

Case Report

An interesting case of mullerian agenesis presenting as adnexal mass

S Bhanu Rekha[1], L Jayanthi Reddy[2]

Mullerian duct abnormalities present at various ages and with varied symptomatology[1]. Partial developmental mullerian anomalies may also present as adnexal lesions creating confusion in the diagnosis like in MRKH syndrome and testicular feminizing syndrome. Removal of dysgenetic gonad has to be done as in cases of testicular feminizing syndrome for the risk of malignancy. In our case the lady had presented with left lower abdominal pain with well developed secondary sexual characters and primary amenorrhea.

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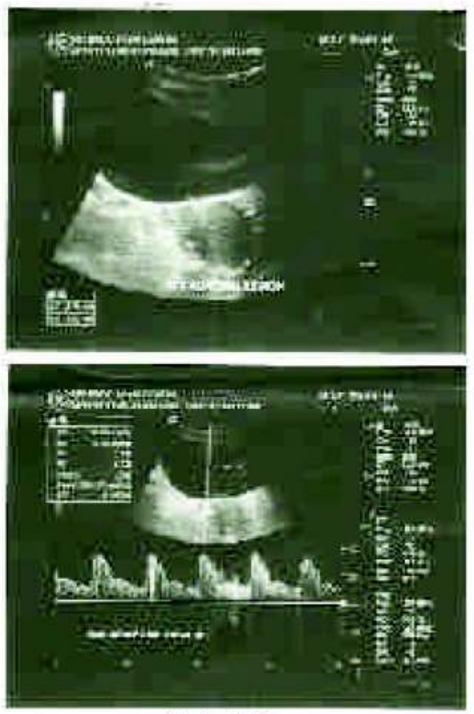
Key words **: Mullerian duct, amenorrhea, MRKH syndrome.**

Many a times adnexal lesions present with pain. In a case of primary amenorrhea, adnexal lesions have to be carefully evaluated as there can be chances of torsion[2], malignant transformation as in dysgenetic gonads or the fear of the ovarian tissue removal in case of MRKH syndrome as it can be the only source of having her genetic child. Though there may be many differential diagnoses in such a scenario, here we present an unusual case of a 27 years old lady with adnexal mass with primary amenorrhea, and chronic lower abdominal pain.

Case Report

A 27 years old nulliparous lady married since 15 years presented to our institute with lower abdominal pain on the left side of 3-4 months duration. Pain was not constantly related to any particular period or time of the month. She had on & off visited the local doctors at the village for symptomatic pain relief. She had no symptoms suggestive of bowel or bladder disturbances. On asking about her menstrual history, she said that she had only few drops of bleeding per vagina at around 13-14 years which was doubtful as she was not confident of it. She had no clear explanation when asked why she had not consulted any gynecologist regarding her amenorrhea. She had been married since 10 years and had no obvious coital difficulties. Her past history & family history were uneventful.

Examination — She was conscious, cooperative, coherent, and comfortable at present. Her height was 158cm & weight was 48 kgs. Thyroid and breast examination was normal. Breast was corresponding to Tanner's stage 4, pubic hair development was also corresponding to stage 4. Her vitals were stable and her systemic examination was also normal. On abdominal examination there was no evidence of any mass, but tenderness was present in the left iliac fossa only on deep palpation. Bowel sounds were normal and there was no evidence of ascites. Her external genital examination showed normal female pattern. On per speculum examination only the lower third of vagina was seen ending blindly. On bimanual examination uterus and cervix was not felt and only lower third of vagina was felt ending blindly. On further examination there was a 4x4 cm globular mass, firm in consistency, slightly mobile felt in the left adnexal site. Per rectal examination confirmed no additional find-



Showing USG Picture

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Showing Karyotyping

ings. On investigating, her routine blood and urine examinations were within normal limits. Renal and Liver functions were normal.

USG abdomen and pelvis were suggestive of the following findings : (1) absent uterus, normal ovaries on both sides and left adnexal complex cyst 4.1x3.2cm with pulsatile index of 2.4 and resistance index of 0.75. S/O benign left adnexal lesion. (2)Three Left renal non- obstructing calculi measuring 8, 10, 11mm and a right renal non- obstructing calculus measuring 4mm. CT abd & pelvis also was suggestive of benign adnexal pathology, with absent uterus.

CA-125 levels were 29.4u/ml. IVP was showing no other associated anomaly except for renal calculi. Her peripheral blood chromosomal analysis showed a normal female karyotype with no structural or numerical abnormalities.

Hence with above findings a probable diagnosis of mullerian agenesis with left ovarian cyst and renal colic was made and decision for laparoscopic cystectomy was planned.

Laparoscopy was done at our institute on 19-12-2011 and to our surprise the following were the findings. Both the fallopian tubes and ovaries were normal .Uterus and cervix was not seen. The left adnexal mass was measuring 4 x 4 cm, with a glistening appearance & was connected by a long ridge like structure to a pea sized mass in the right adnexa (Figs 1 & 2).

A conclusion that the mass was left rudimentary uterus and a small pea sized right rudimentary horn with no possibility of any menstrual or reproductive function was made and option of removal was given to the family. But the family members failed to give consent for the removal of rudimentary left horn in spite of counseling regarding the non functioning cornu and chances of increasing in the size of the mass and chances of having genetic child by surrogacy. Hence the operation was abandoned. She was lost for follow up after discharge from hospital.

Discussion

Uterine developmental anomalies are thought to be rare as the

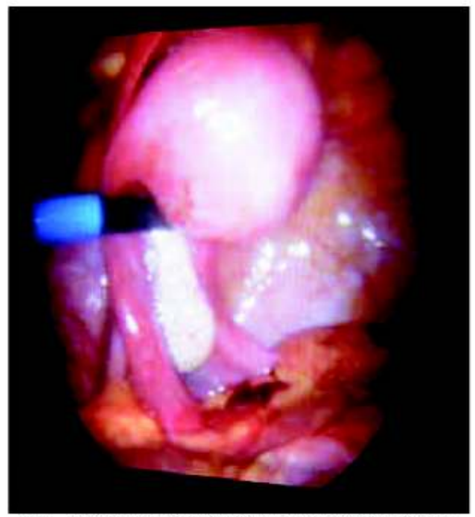

Fig 1 — Showing left rudimentary horn with normal adnexa (4x4 cm)

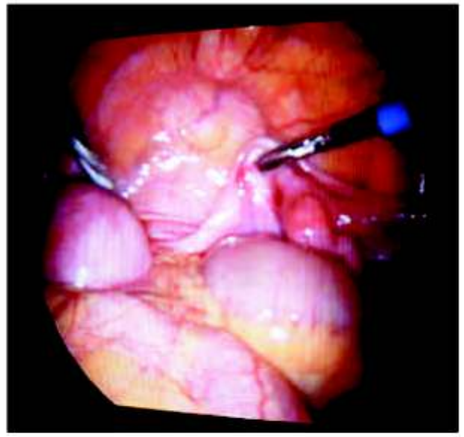

Fig 2 — Right pea sized rudimentary horn connected by a ridge like tissue to the left 4x4 rudimentary horn

incidence is around 0.1%, though observations made during deliveries and hysterectomies increase the incidence to up to 2- 3%. The exact causes of uterine anomalies though not clearly known, may be due to genetic, environmental (as in DES exposure) or both[1]. According to WHO classification, the uterine anomalies are categorized as follows :

(1) Hypoplasia or agenesis
(2) Unicornuate uterus
(3) Uterus Didelphys
(4) Uterus Bicornuate

(Continued on page 30)

Case Report

Gliosarcoma : a rare variant of glioblastoma multiforme

Kirti Rathod[1], Menka Shah[2], Kalpesh Shah[3], Monica Gupta[4]

Gliosarcoma is biphasic intraaxial malignant neoplasm of the central nervous system and rare variant of Glioblastoma Multiforme (GBM). Gliosarcoma constitute approximately 2% of all glioblastoma multoforme. Here we present a case report of 32 year-old gentleman presented with a history of right-sided weakness and slurred speech. Brain imaging (CT scan and MRI) was suggestive of a right frontal mass lesion with contrast enhancement at the periphery. Histopathological diagnosis was gliosarcoma that was further confirmed by immunohistochemically.

[*J Indian Med Assoc* 2018; **116**: 29-30]

Key words **: Gliosarcoma, Biphasic, Glioblastoma Multiforme.**

Gliosarcoma is a rare variant of Glioblastoma Multiforme. Gliosarcoma corresponds histologically to WHO Grade IV astrocytoma. We present a case of gliosarcoma and review the literature of this uncommon clinical entity.

Case Report

A 32 year-old gentleman presented with a history of right sided weakness and slurred of speech. On examination, he had right hemiparesis grade 4/5 and slurred speech.

Investigations — CT scan showed a left fronto-parietal isodense lesion with marked peripheral edema in the left frontal region; peripheral enhancement was noted after administration of contrast. On MRI the lesion was hypointense on T1- and hyperintense on T2-weighted images, and was irregularly enhancing with contrast. Total surgical excision was undertaken.

Histopathology — The histopathology examination revealed a malignant brain tumour presenting a biphasic tissue pattern with gliomatous and mesenchymal components. The glial component was similar to a glioblastoma with nuclear pleomorphism, high mitotic index, marked vascular proliferation and foci of necrosis (Fig 1, H & E, 10 x).

The mesenchymal component consists of areas with densely packed long bundles of spindle cells in a storiform pattern .

Reticulin stain positive in the sarcomatous component.

Immunohistochemically, Gliomatous areas showed glial-fibrillary acidic protein expression (Fig 2, IHC, 40x). The sarcomatous cells expressed vimentin.

Discussion

Gliosarcomas constitute approximetely 2% of all glioblastomas[1,2]. The age distribution is similar to that of the primary glioblastomas, with preferential manifestation between ages 40 and 60. Males are frequently affected.

Gliosarcomas are usually located in the cerebrum, involving the temporal, frontal, parietal and occipital lobes in decreasing order of frequency[5].

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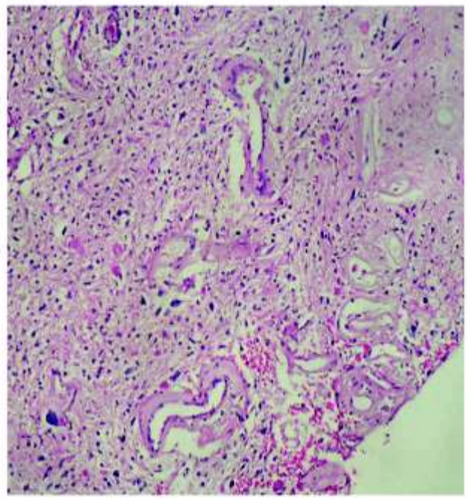

Fig 1 — Microphotograph shows gliomatous component

The clinical history is usually short. Most of patient present with seizures and paresis.

Macroscopically the sarcomatous component produces a firm, often superficial, discrete mass in a lesion.

Histopathologically, Gliosarcomas are characterized by a biphasic pattern with areas of both glial and sarcomatous components[6]. The glial portion usually shows the typical features of a glioblastoma with a varying degree of anaplasia and GFAP expression. The sarcomatous areas often show the typical herringbone pattern of fibrosarcoma, with densely packed long bundles of spindle cells. Occasionaly, the histology resembles features of a malignant fibrous histiocytoma[2,3]. For diagnosis purposes, the demonstation of reticulin in the sarcomatous component and GFAP in the gliomatous portion is important[4]. Gliosarcoma may show a variety of ad-

ditional lines of mesenchymal differentiation. Epithelial metaplasia with clusters of keratinizing stratified epithelium and adenoid formation have been noted[7].

Gliosarcoma show similar genetic aberrations to those occurring in glioblastomas. Clinical trials have failed to demonstrate a difference in outcomes for gliosarcoma and GBM.

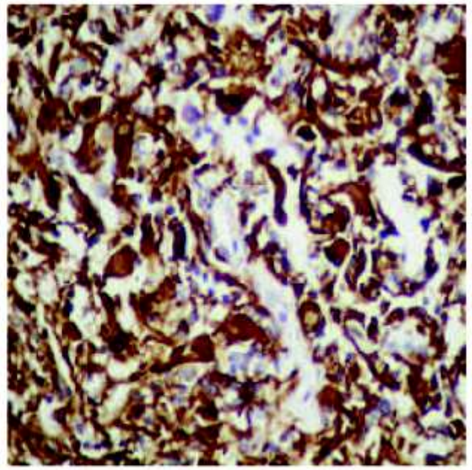

Fig 2 — Immunohistochemical microphotograph show GFAP positive gliomatous components

References

1 Feigin I, Gross SW — Sarcoma arising in glioblstoma of the brain. *Am J Pathol* 1955; **31:** 633-53.
2 Meise JM,Martz KL, Nelson JS — Mixed glioblastoma multiforme and sarcoma. A clincopathologic study of 26 radiation therapy oncology group cases. *Cancer* 1991; **67:** 2342-9.
3 Ng HK, Poon WS — Gliosarcoma of the posterior fossa with features of a malignant fibrous histiocytoma. *Cancer* 1990; **65:** 1161-6.
4 Meise JM, Ho KL, Nelson JS — Gliosarcoma: a histologic and immunohistochemical reaffirmation. *Mod Pathol* 1990; **3:** 19-24.
5 Paul K, Webster K — Cavenee, Who Classification of Tumours of the Nervous System 2000; 42-4.
6 Stacey E. Millis, Darryl Carter, Joel K Greenson, Harold A Oberman — Sternberg' Diagnostic Surgical Pathology, 4th edition, 2004, 446.
7 Rosai and Ackerman's Surgical Pathology, Ninth edition, 2004, 2536-7.

(Continued from page 28)

(5) Septate uterus
(6) Arcuate uterus
(7) DES related

The commonest uterine anomalies are Septate and bicornuate uterus. Many a times the uterine anomalies are usually asymptomatic until the age of menarche or until pregnancy is attempted. They either present with primary amenorrhea (as in uterine agenesis) or abdominal pain or dysmenorrhea[3,4] (due to menstrual blood getting collected in the rudimentary horn), dyspareunia[5] or reproductive problems (like ectopic pregnancy, recurrent pregnancy loss or recurrent malpresentations).

The uterine anomalies can be diagnosed by pelvic examination or by other investigations like USG, HSG, Sonosalpingogram, MRI, hysteroscopy, Laparoscopy.

The treatment aspect depends on the type of uterine anomaly and involves mainly surgical correction in most of the cases.

In our case the lady had presented with left lower quadrant abdominal pain and primary amenorrhea. The cause was identified as partially developed rudimentary horn which was mistaken for left ovarian cyst before going for laparoscopy.

References

1 Tarannum M, Diane L — Amenorrhea: Evaluation and Treatment. *Am Fam Physician* 2006; **73:** 1374-82.
2 Sari L, Sheldon J — Mullerian agenesis and ovarian torsion. A case report and review of literature. *J Pediatr Surg* 2005; **40:** 1326-8.
3 Agarwal M, Das A, Singh AS — Dysmenorrhea due to a rare mullerian anomaly. *Niger J Clin Pract* 2011; **14:** 377-9.
4 Goluda M, St Gabrys M, Ujec M — Bicornuate rudimentary uterine horns with functioning endometrium and complete cervical – vaginal agenesis co-existing with ovarian endometriosis. *Fertilsteril* 2006; **86:** 462e9-11.
5 Fiona MB, Julie M — An observational study of women with mullerian agenesis and their need for vaginal dilator therapy. *Fertilsteril* 2011; **96:** 483-6.

Special Supplement on CARDIOLOGY

Editorial

Heart Care in 21st Century

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Before 1970, cardiologists used to be physicians with special interest in the treatment of heart diseases. In 50 years time, today, cardiology is an independent speciality with multiple divisions like noninvasive, invasive/interventional cardiology, electrophysiology, heart failure as speciality, paediatric cardiology and molecular cardiology etc.

It is indeed American Heart Association (AHA), National Heart Lung and Blood Institute (NHLBI), Framingham Heart Study, whose enormous contribution led to the development of today's cardiology.

Establishment of coronary care unit, thrombolytic therapy in acute myocardial infarction, β-blockers, angiotensin converting enzyme inhibitors, pacemakers, defibrillators have significantly improved survival of heart patients. Cardiovascular imaging of heart and great vessels, echocardiography, nuclear scan, CT scan, MRI, angiography, have improved the precision of understanding of cardiovascular disease pathology. Similarly angioplasty, stents, cardiac resynchronization therapy (CRT), aspirin, newer antiplatelets and anticoagulant agents, have saved many lives.

Evidence based treatment of hypertension, dyslipidaemia, diabetes mellitus, clearly reduced the incidence of stroke, myocardial infarction and heart failure hospitalizations. Cardiac surgery for congenital and acquired heart diseases, artificial heart valves, coronary artery bypass surgery (CABG), off pump heart surgery, port access surgery, heart transplantation, and more recently robotic vascular interventions, have elevated care of cardiac patients to a magnificent level. The advances in development of ventricular assist device (VAD) have been phenomenal. Catheter based valve inplantation of aotic valve and mitral valve repair show remarkable success in cardiology. The Human Genome project has shown that 80% of cardiovascular deaths are due to 20 diseases. Genetic causes have been established for Wolff-Parkinson-White (WPW) syndrome, Long QT syndrome, hypertrophic cardiomyopathy and familial hypercholesterolaemia. Gene therapy is getting established. Heart failure management today is achieving a new altitude.

Nevertheless today cardiovascular care is going through a double barrel challenge. On one side, there is ceaseless, ongoing development of technologies to diagnose and alleviate heart ailments and on the other side, there is prohibitive cost to implement these facilities to our patients. Heart care economics is a formidable impediment in application of these advancements for heart disease treatment.

During the forthcoming 50 years, perhaps from the divergence of cardiovascular specialists, physicians and surgeons contributing untiringly towards the wellness of human heart will enter into an emerging epoch of convergence where physicians, surgeons, interventionists, image specialists, electrophysiologists robot experts will be together in a common suite, working in harmony.

Human heart will find a life which would perhaps be just short of existent immortal.

Original Article

Is there any gender related difference existing in the presentation or management of patients with acute pulmonary embolism ? A prospective study

Soumya Patra[1], Rabin Chakraborty[2]

Acute pulmonary embolism is an important cardiovascular cause of morbidity & mortality in general population. Whether gender has any implication in the clinical presentation and management of these patients is unclear. The objective of this study was to compare the clinical presentation and the therapeutic benefit in women and men with acute pulmonary embolism. In this study, 142 male & 85 female patients with acute pulmonary embolism were included and the clinical presentation and course after therapy were observed and compared. Results: Mean age of the study group (43.6 ± 14.7 *versus* 44.2 ± 13.9 years, p=0.66) and mean duration of symptoms (4 ±2 *versus* 6 ±4.4 days, p=0.04) before presentation in male patients were less than female patients. There were no significant differences seen in functional class, hypotension, electrocardiographic & echocardiographic features based on gender. Though there was non-significantly more death (13% *versus* 10%, p=0.74) but significantly more incidence of minor bleeding (25% *versus* 8%, p=0.045) in female patients than male patients. Other than increased incidence of minor bleeding, there were no significant differences in the clinical presentation, therapeutic benefit, and course after therapy, therefore, gender should not influence the decision to treat pulmonary embolism patients especially with thrombolytic agents but extra caution has to be taken while treating female patients. [*J Indian Med Assoc* 2018; **116:** 32-4 & 49]

Key words **: Acute; gender, pulmonary embolism, thrombolytic therapy.**

Acute pulmonary embolism (PE) is the third most common acute cardiovascular disease after myocardial infarction and stroke. The incidence of acute PE is increasing in the general population[1]. In a previous study, it was demonstrated that gender has not any influence in the presentation or management of patients with PE[2]. Another study however, concluded that women with sub massive PE, have less benefit and more complication following thrombolytic therapy[3]. It is still unclear, whether gender has any impact in the clinical presentation and management of PE. We conducted this prospective observational study to compare the clinical presentation, therapeutic benefit of treatment, course after treatment and complication in women and men with acute pulmonary embolism.

Material and Methods

Study Design : It was a prospective observational study. This study was conducted in a tertiary cardiac care institution in the last two years.

Eligibility Criteria :

Inclusion criteria: Patients of age more than 18 years with Acute PE (first symptoms 15 d or less before presentation) and confirmed by a positive findings in CT pulmonary angiogram (CTPA) or through echocardiography were included.

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Exclusion criteria : Patients were excluded from the study those who have the following criteria

(1) Symptoms started more than 15 days.

(2) Administration of a thrombolytic agent in the previous 4 d or glycoprotein IIb/IIIa antagonists within the preceding 7 days.

(3) Vena cava filter insertion or pulmonary thrombectomy in the previous 4 days.

(4) Uncontrolled hypertension (systolic BP >180 mm Hg and/or diastolic BP >110 mm Hg at presentation).

(5) Known hypersensitivity to STK, TNK or heparin.

(6) Known coagulation disorder (including use of vitamin K antagonists and platelet count <100,000/mm^3).

(7) Clinically relevant bleeding within the last 6 months or if they had a hemorrhagic diathesis, active peptic ulcer, arterial aneurysm or arterial/venous malformation, cancer at increased risk for bleeding, history of stroke, intracranial or spinal surgery.

(8) Major surgery, biopsy or trauma in the 2 months preceding the admission.

(9) Had prolonged cardiopulmonary resuscitation (>10 minutes) in the last two weeks.

Ethics : The study protocol was approved by the Ethics Committee of the respective authority of our institution. Written informed consent was obtained from all patients, before inclusion in the study.

Methods : Written proformas will be filled up during inclusion of patients which will contain epidemiological information (age, sex, occupation, and place), questionnaires for risk factor evaluation (smoking, drug history, malignancy, comorbid condition, hypercoagulable state), information of clinical presentation (dyspnea, chest pain, syncope, cardiac arrest, etc) and clinical signs. Those patients had diagnosed acute PE, was treated as per unit protocol with either thrombolytic agent tenecteplase or streptokinase followed by unfractionated heparin (UFH) injection or UFH alone. All the patients were prospectively studied; data was collected, compiled and analysed.

Investigations : All patients will be investigated with the following tests;

(1) Chest X-ray

(2) Electrocardiogram: For all patients, standard 12-lead ECG was recorded on admission with a paper speed of 25 mm/s. The first available ECG was used for analysis.

(3) Echocardiography: Baseline echocardiography was to be done within 24 hours from the diagnosis of PE. For the purpose of this study, right ventricular dysfunction (RVD) was defined as the right/left ventricle end-diastolic dimension ratio >1 in the apical 4-chamber view and/or >0.7 in parasternal long axis, both in the absence of right ventricle hypertrophy. Echocardiography was scheduled to be repeated 24 hours and at discharge or 7 days after study treatment administration. The pulmonary artery systolic pressure (PASP) was calculated by using tricuspid valve regurgitation jet & inferior vena cava dimension.8

(4) d-Dimer test/ Troponin T assay

(5) CTPA

(6) Complete Hemogram, Bleeding time (BT), Clotting time (CT), Prothrombin time (PT) & activated plasma thromboplastin time (aPTT), Renal function test, Liver function test.

(7) Doppler Venography/ ultrasound abdomen if necessary

Outcomes : Patients were evaluated on the day of discharge and theoutcome in this study was to determine the clinical improvement following thrombolysis which was defined as improvement in the New York Heart Association (NYHA) class, dyspnoea, tachycardia, hypoxemia, and improvement in general well being along with reduction of RVD and/ or PASP seen at echocardiography.

Complication : This was as follows: (1) composite of death from any cause, (2) Hemodynamic collapse is defined as at least 1 of the following: (i) the need for cardiopulmonary resuscitation; (ii) systolic blood pressure <90 mm Hg for at least 15 minutes, or drop of systolic blood pressure by at least 40 mm Hg for at least 15 minutes, with signs of end-organ hypoperfusion (cold extremities, or urinary output <30 mL/h, or mental confusion); (iii) the need for catecholamines (except for dopamine at a rate of <5 µg kg-1 min-1) to maintain adequate organ perfusion and a systolic blood pressure of >90 mm Hg, (3) ischemic or hemorrhagic stroke within 7 days, and (4) bleeding (ie, minor or severe) within 7 days. Minor bleeding defined as a bleeding not requiring blood transfusion. Severe bleeding is defined as an episode that leads to hemodynamic compromise requiring emergency intervention (as administration of fluids and/or blood products, inotropic support, or surgical treatment), or is life threatening, or fatal.

Statistics : All the data was compiled at the end of the study and the sample was analyzed with Chi-square. The p value of <0.05 will be considered as statistically significant.

Results

Since last two years, 227 patients were admitted in our hospital with the clinical diagnosis of acute PE. Among them, 142 patients were male and rest 85 patients were female.

Baseline characteristics of patients at presentation: Table 1 demonstrated the baseline characteristics of our study patients. There was significant difference seen in the duration of symptoms before admission. It was less in male patients than in female patients (4 ±2 *versus* 6 ± 4.4 days, p=0.04) and it is due to less health care seeking behaviour among female in our country. Other than smoking which was more commonly seen among male patients, there were no significant differences seen in mean age, risk factors and presenting symptoms among the study patients. After admission, mean systolic blood pressure (111±22 *versus* 116± 23 mm of Hg), hypoxia (39% *versus* 47%)and tachycardia (60% *versus* 66%) was seen less frequently and hypotension (27% *versus* 25%) was more common in male patients than female patients without having any statistical significance. There was no statistically significant differences seen in blood investigation, electrocardiogram (ECG) & echocardiographic parameters which was in similar agreement with the previous studies[3-4]. Though mean PASP was more at baseline (66 ± 22.1 *versus* 63 ± 21.2 mm of Hg) and RVD (92% *versus* 90%) was also seen more frequently in male patients than in female patients, but both the results were statistically insignificant. More number of male patients in our study group received streptokinase (72% *versus* 59%) though tenecteplase (13% *versus* 14%) & only UFH (15% *versus* 27%) were given more in female patients, but all these results didn't have any statistical significance.

Clinical course after therapy: Table 2 demonstrated the results of clinical course after therapy. Persistently elevated PASP of > 30 mm of Hg (20% *versus* 19%), improvement in functional class (88% *versus* 87%) and clinical improvement (72% *versus*. 67%) were seen insignificantly more commonly in male patients than in female patients.

Complications after therapy: Table 3 showed the results of complication after receiving treatment in both male & female patients. Though duration of stay in intensive care unit (ICU) was almost similar in both the groups but

Table 1 — *Baseline characteristics of patients according to their gender*

Variable	Male (n=142)	Female (n=85)	P value
Age (mean)	43.6 ± 14.7 years	44.2 ± 13.9 years	NS
Risk factors :			
Smoking	70 (49%)	02 (02%)	P<0.01
DVT	47 (33%)	32 (38%)	NS
Obesity/ dyslipidemia	25 (18%)	18 (21%)	NS
H/O recent surgery/Bedridden	26 (18%)	25 (29%)	NS
No apparent risk factors	47 (33%)	31 (36%)	NS
Duration of symptoms at presentation (mean)	4±2 days	6 ±4.4 days	P=0.04
Presenting complaints :			NS
Dyspnoea	126 (89%)	81 (95%)	NS
Chest pain	88 (62%)	36 (42%)	NS
Syncope	22 (15%)	10 (12%)	
NYHA class :			
Class I/II	19 (13%)	7 (8%)	NS
Class III	110 (77%)	61 (72%)	NS
Class IV	13 (10%)	17 (20%)	NS
Clinical features :			
Mean SBP	111±22 mm Hg	116± 23 mm Hg	NS
Hypotension	37 (27%)	21 (25%)	NS
Tachycardia	85 (60%)	56 (66%)	NS
Hypoxia (SpO_2<92% in room air)	55 (39%)	40 (47%)	NS
Investigations :			
d-Dimer	39 (27%)	30 (35%)	NS
Toponin T/ CKMB	48 (34%)	27 (32%)	NS
Abnormal Chest x-ray	38 (27%)	17 (20%)	NS
Electrocardiogram (ECG) features :			
Sinus tachycardia	81 (57%)	49 (58%)	NS
RBBB	29 (20%)	10 (12%)	NS
S1Q3T3	64 (45%)	35 (41%)	NS
'T' inversion mid chest leads	77 (54%)	37 (44%)	NS
Right axis deviation/ RVH with strain	60 (42%)	33 (39%)	NS
Baseline Echocardiography :			
PASP (mean)	66±22.1 mm Hg	63±21.2 mm Hg	NS
RVD	130 (92%)	77 (90%)	NS
Treatment :			
Streptokinase	103 (72%)	50 (59%)	NS
Tenecteplase	18 (13%)	12 (14%)	NS
Inj. UFH only	21 (15%)	23 (27%)	NS

female patients had more death (13% *versus*. 11%), clinical deterioration (20% *versus* 18%) and minor bleeding (12% *versus* 8%) following treatment with either thrombolytic agents or anticoagulant medication, but all these results were statistically insignificant.

Discussion

Our study was a prospective observational study from a single centre with adequate number of patients with acute PE. Here, in this study, we have observed any difference in the clinical presentation, investigations along with response, course & complication after treatment among the male & female patients. So far only few studies had tried to find out this gender related differences in the patients of acute PE[2-3]. We also tried to compare any gender based differences while managing a patient with acute PE. Other than duration of symptoms before presentation and smoking, all other clinical, blood investigations, radiological investigations and echocardiographic parameters were similar in both male & female patients. These observations were similar with the

Table 2 — *Clinical course after therapy*

Variable	Male patients (n=142)	Female patients (n=85)	P value
Abnormal PASP (>30 mm Hg)	28 (20%)	16 (19%)	NS
Clinical Improvement	102 (72%)	57 (67%)	NS
NYHA class at discharge :			
Class I/II	125 (88%)	74 (87%)	NS
Class III	14 (10%)	9 (11%)	NS
Class IV	3 (2%)	2 (2%)	NS

Table 3 — *Complication after therapy & duration of ICU stay*

Variables	Male patients (n=142)	Female patients (n=85)	P value
Adverse events :			
Death	15 (10%)	11 (13%)	NS
Clinical deterioration	25 (18%)	17 (20%)	NS
Development of Hypotension	16 (11%)	7 (8%)	NS
Mild bleeding	12 (8%)	10 (12%)	NS
Major bleeding (including Stroke)	2 (1%)	1 (1%)	NS
Duration of ICU stay (mean)	2±0.5 days	2±0.8 days	NS

previous studies[2-4]. Though in this study, we have included all patients with acute PE without differentiating whether they had massive or submassive PE. This was not done in the previous multi centre study where large numbers of patients with sub massive PE were enrolled[3]. There was almost similar distribution of patients according to their treatment received. In our study, we had taken short term observation up to day of discharge of our patients than up to 30 days which was done in a previous study[3]. The duration of hospital stay was similar in both male & female patients which was in agreement with a previous study, though there were gender-related differences reported with regard to the recurrence of venous thromboembolism over the long term.5 The clinical improvement and improvement in the functional class at discharge were almost similar in both men & female which was in agreement with few previous studies[2,6] and disagreement with a recent study[3]. Thedeath rate was insignificantly more in female and this result was similar with the previous studies[2-3]. Though there was insignificantly more cases with minor bleeding manifestation seen following thrombolytic therapy in female patients but overall the adverse events were similar in both the study groups following treatment. This observation was also similar with a previous study[2] and disagreement with another study[3].

As this was an observational study so this result shouldn't be generalized and we have treated both massive & sub massive PE with thrombolytic therapy which is according to the few recent trials[7-10] though treatment of sub massive PE with thrombolytic therapy is so far not indicated in the guidelines[11-12].

With keeping all these limitations in mind, our observations suggest that there should not be any gender related bias while managing a patient with acute PE especially with thrombolytic agents, though further large randomized trial is needed to resolve this debate in future.

Funding and conflict of interest : None.

(Continued on page 49)

Review Article

Heart and the mind : depression and cardiovascular disease

Anindita Chakraborty[1], H Yavuz Yince[2], Stromberg Nicole[3]

Depression is highly prevalent in patients with cardiovascular disease (CVD) and is associated with poor quality of life, poor medication adherence and higher cardiovascular morbidity and mortality. Though the American Heart Association (AHA) association recommends universal screening, there is currently no evidence to suggest that universal screening improves cardiovascular outcomes. That being said, physicians must be aware of risk of depression in this vulnerable population and screen when depression is suspected. To be effective, screening must be paired with appropriate referral or collaborative care. Patients with a positive screen, may be monitored and treated by a mental health professional. Treatment of depression improves mood and quality of life, though more research is needed to determine if treatment of depression in CVD improves cardiovascular outcomes.

[*J Indian Med Assoc* 2018; **116**: 35-8]

***Key words* : Depression, Cardiovascular disease.**

Mr S, a 65 year old man with a history of hypertension, type 2 diabetes and cigarette smoking came in to clinic with chest pain and shortness of breath upon exertion. Upon taking a history, his doctor found that Mr. S had been non-adherent to his medications for diabetes and hypertension. His electrocardiogram (EKG) was unremarkable but a stress test revealed signs of ischemia. His echocardiography showed normal left ventricular function with no wall motion abnormalities. Coronary angiography revealed a significant lesion at the proximal left anterior descending artery (LAD). Mr S underwent coronary angioplasty and received a stent to LAD. His discharge medications included aspirin, atenolol, lisinopril, atorvastatin and metformin. His doctor also recommended secondary prevention measures such as diet and exercise interventions and smoking cessation. Upon discharge, Mr S followed up intermittently but disappeared from follow up for several years, until one day he presented to the emergency department with acute onset chest pain and shortness of breath. On admission to the hospital his troponin I was elevated and EKG was suggestive of Anterior wall ST segment myocardial infarction (STEMI). This time coronary angiogram revealed critical stenosis at the left main coronary artery and a stent was placed. At one month follow up he revealed symptoms of low mood, loss of interest in life and fatigue that began 2 years prior to his diagnosis of heart disease. A diagnosis of major depression was made and Mr S was referred to a psychiatrist.

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Is Depression A Risk Factor For Recurring Cardiac Events ?

Depression is present in one in 5 patients with CVD a prevalence that is at least 3 times greater than in the general population[1]. Though the prevalence of depression in CVD is higher in women, cardiac prognosis in worse for men[2]. Patients with depression and CVD are more likely to have physical limitations and poor quality of life, which are independent of measures of cardiac function such as left ventricular ejection fraction[1]. Patients with CVD and co-morbid depression are at increased risk for adverse cardiovascular outcomes independent of traditional risk factors such as diabetes, hypertension, cigarette smoking, obesity, hypercholesterolemia and left ventricular ejection fraction[3].

For example after one attack of myocardial infarction (MI), depressed patients have double the risk of cardiovascular events over the next 1-2 years, after accounting for traditional risk factors[4].

In terms of the course of illness, depression in CVD is often chronic and recurrent, in hospitalized patients with CVD approximately 50-70% of patients developed symptoms of depression prior to their cardiac event[5]. Symptoms of depression post MI might be viewed as a normal reaction to stress and be expected to remit spontaneously. In fact, spontaneous remission occurs in about half of cases of post-MI depression, while the other half will either persist or remit only to relapse within a year[6].

Is Depression A Risk Factor of New Onset CVD ?

Yes. There is also evidence to suggest that depression alone is a risk factor for new onset CVD. One meta-analysis of 30 prospective cohort studies (N=8,93850) found that individuals with depression compared with non depressed individuals experience a significantly increased risk of 30% for CVD[7].Another meta-analysis of prospective studies found that depression was associated with a 31% increase in risk for myocardial infarction (MI) and a 36% increase in coronary death compared with non depressed persons[8].

What is the Link Between Depression and CVD?

Both physiological and behavioral factors have been explored in the relationship between depression and heart disease.

With respect to behavioral factors, we already know that medication non-adherence and low physical fitness are associated with adverse cardiovascular outcomes. Depressed patients are less likely to engage in preventative behaviors such as smoking cessation, physical exercise and adherence to medications. One study found that depression is an independent predictor of medication non-adherence in patients with CVD[9]. In another study of depressed patients it has been shown that while they were hospitalized for cardiac conditions, adherence to diet, exercise and medication improved if their depression did improve[10].This may suggest that treating depression may promote preventative behaviors as well.

Numerous inter-related physiological factors have been proposed. While the role of inflammation in atherosclerosis has been well studied, depression has also been associated with increased inflammatory cytokines (such as IL-6, IL-1, CRP) Inflammation along with other mechanisms promote endothelial dysfunction which may contribute to myocardial ischemia[2]. Platelet dysfunction and abnormal blood serotonin levels are known to occur independently in patients with depression and in those with CVD. It is well known that serotonin binds to 5 Hydroxy Tryptamine (5-HT) receptors and leads to platelet aggregation. By depleting platelet serotonin stores antidepressants like selective serotonin reuptake inhibitors (SSRI) (antidepressants) have been shown to decrease platelet aggregation in vitro[2].This raises a fascinating question of whether antidepressants may be helpful to prevent myocardial damage.

Many more mechanisms exploring the link between CVD and depression have been postulated (Fig 1).

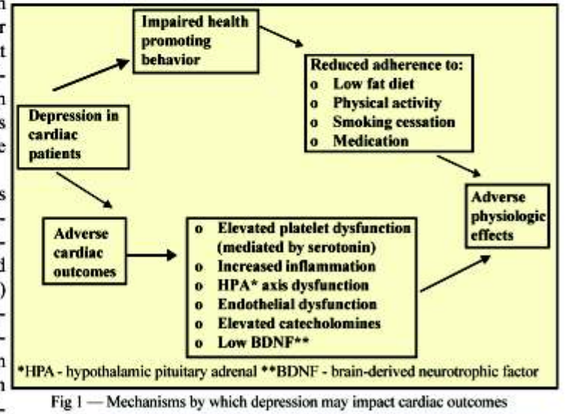

Fig 1 — Mechanisms by which depression may impact cardiac outcomes

Table 1 — *Patient Health Questionnaire: 2 Items**

Over the past 2 weeks, how often have you been bothered by any of the following problems?
(1) Little interest or pleasure in doing things.
(2) Feeling down, depressed, or hopeless.

*If the answer is "yes" to either question, then refer for more comprehensive clinical evaluation by a professional qualified in the diagnosis and management of depression or screen with PHQ-9.

Diagnosis of Depression In Cardiovascular Disease : To Screen Or Not To Screen ?

Due to the high prevalence of depression in patients with CHD, the American Heart Association (AHA) supports a strategy of routine screening in various settings including hospitals and clinics[4] (Fig 2). Screening may be performed by the Patient Health Questionnaires (PHQ), a self-administered tool, that takes less than 2 minutes to complete, it is free of cost and available in multiple different languages online. At a minimum the PHQ-2 (consisting of 2 screening questions) is recommended to identify current depression (Table 1). A negative PHQ-2 ends the screening process. A positive PHQ-2, should be followed by a PHQ-9 (Table 2). A PHQ-9 yields a provisional diagnosis of major depression and a severity score that can used to guide monitoring and treatment. Critics however, remain skeptical about universal screening guidelines, due to concerns of misallocation of limited resources, misdiagnosis and improper delivery of care in those diagnosed with depression.

There is evidence to suggest that routine screening performed in the setting of collaborative care models may improve symptoms of depression, reduce cardiac symptoms and reduce cardiac events, though more studies are needed to corroborate these findings[2,11,12]. Therefore, if screening is performed, it is to be paired with some management protocol such as referral to a trusted psychiatrist or better still establishing collaborative care between the patients' general practitioner, cardiologist, psychiatrist and other psychosocial supports[2].

Table 2 — *Patient Health Questionnaire-9 (PHQ-9)* Depression*

Screening Scales Over the past 2 weeks, how often have you been bothered by any of the following problems?
(1) Little interest or pleasure in doing things.
(2) Feeling down, depressed, or hopeless.
(3) Trouble falling asleep, staying asleep, or sleeping too much.
(4) Feeling tired or having little energy.
(5) Poor appetite or overeating.
(6) Feeling bad about yourself, feeling that you are a failure, or feeling that you have let yourself or your family down.
(7) Trouble concentrating on things such as reading the newspaper or watching television.
(8) Moving or speaking so slowly that other people could have noticed. Or being so fidgety or restless that you have been moving around a lot more than usual.
(9) Thinking that you would be better off dead or that you want to hurt yourself in some way.

*Questions are scored: not at all=0; several days=1; more than half the days=2; and nearly every day=3. Add together the item scores to get a total score for depression severity.

Treatment of Depression In Cardiovascular Disease : Will It Prevent Future Cardiovascular Events ?

Treatment of depression in heart disease includes antidepressant medications and psychotherapy based on patient preference and available resources. Before referral to a psychiatrist, patients must be provided psychoeducation on depression, as the diagnosis is often associated with stigma and denial. SSRIs remain first line in the treatment of depression all of which are equal in efficacy. Out of psychotherapy modalities, cognitive behavioral therapy

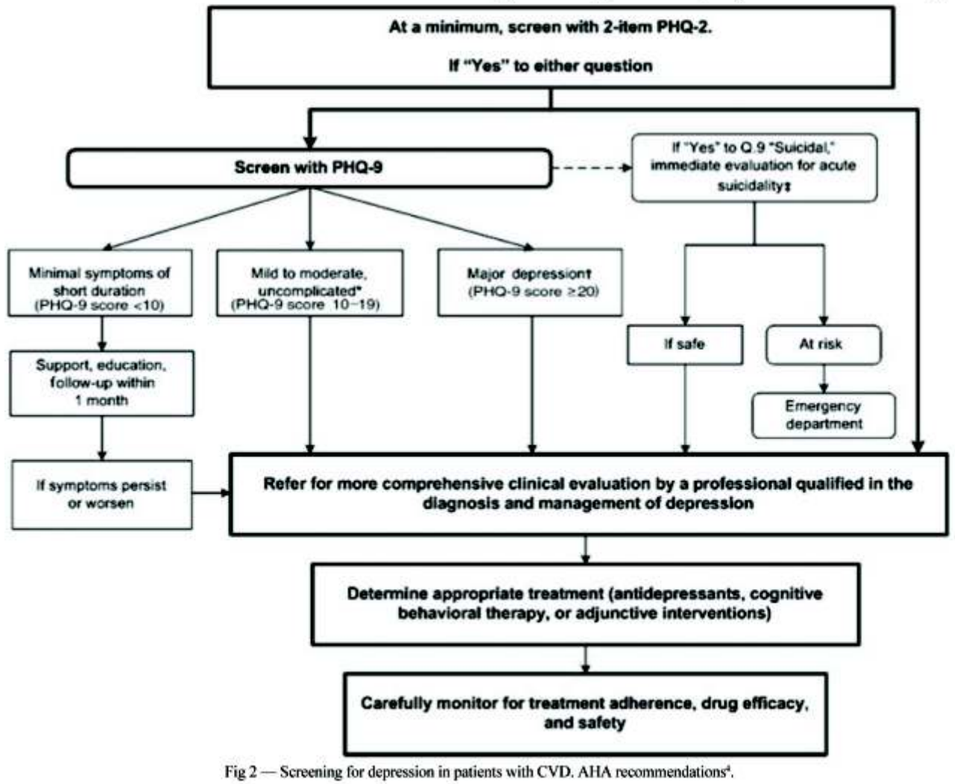

Fig 2 — Screening for depression in patients with CVD. AHA recommendations[4].

(CBT) is considered to be the most effective in treating depression. Treatment of depression requires time, antidepressants take 3-4 weeks to start working and CBT requires regular attendance for at least 12 weeks. Depression must be treated as it improves mood and quality of life. Patients recovering from depression are more likely to adhere to medications, diet and exercise regimens and more likely to enlist the support of family and friends[13].

Whether treatment of depression improves cardiovascular outcomes is unknown at this time. To date, there are few randomized control trials comparing antidepressants vs. placebo and their impact on long term cardiovascular outcomes. Though the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) was designed the test the safety and efficacy of Sertraline in post ACS depression, it did find a statistically non-significant reduction in adverse cardiovascular events in the Sertraline group[6]. A Korean study comparing Escitalopram vs. Placebo in post ACS depression found a statistically significant reduction in adverse cardiovascular events after 8.1 median years of follow up. This is the first randomized control trial that proves a causal association between CVD and depression[14]. These results are intriguing as SSRIs are known to reduce platelet activation. We need more randomized control trials to generalize these findings. In terms of psychotherapy, the Enhancing Recovery in Coronary Heart Disease (ENRICHD) was a randomized control trial that studied the effects of CBT vs. usual care in patients with post ACS depression. While investigators showed that 12 weeks of CBT allowed remission of moderate to severe depression, there was no difference in event free survival between the 2 study groups[15]. It is important to note that all the above trials were conducted in the post MI period where somatic symptoms may make diagnosis of depression more challenging. In order to fully understand whether treatment of depression improves cardiovascular outcomes there is need for more randomized control trials at different points on the spectrum of CVD.

In the above case, Mr. S's depression was present 2 years prior to the presentation of his CVD and depression was diagnosed only after he had an MI. Was depression a risk factor for his MI? If yes; would diagnosing and treating his depression earlier could have prevented his heart attack? We do not know that yet. What we do know is that treating depression would have improved his symptoms and quality of life. Physicians therefore, should consider mind disorders as important components while treating heart patients.

References

1 Cohen BE, Edmondson D, Kronish IM — State of the art review: depression, stress, anxiety, and cardiovascular disease. *American Journal of Hypertension* 2015; **28:** 1295-302.

2 Huffman JC, Celano CM, Beach SR, Motiwala SR, Januzzi JL — Depression and cardiac disease: epidemiology, mechanisms, and diagnosis. *Cardiovascular Psychiatry and Neurology* 2013; 2013.

3 Lichtman JH, Froelicher ES, Blumenthal JA, Carney RM, Doering LV, Frasure-Smith N, *et al* — Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: systematic review and recommendations: a scientific statement from the American Heart Association. Circulation. 2014 Jan 1:CIR-0000000000000019.

4 Lichtman JH, Bigger Jr JT, Blumenthal JA, Frasure-Smith N, Kaufmann PG, Lespérance F, *et al* — Depression and coronary heart disease: recommendations for screening, referral, and treatment: a science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Psychiatric Association. *Circulation* 2008; **118:** 1768-75.

5 Glassman AH, Bigger JT, Gaffney M, Shapiro PA, Swenson JR — Onset of major depression associated with acute coronary syndromes: relationship of onset, major depressive disorder history, and episode severity to sertraline benefit. *Archives of General Psychiatry* 2006; **63:** 283-8.

6 Glassman AH, O'connor CM, Califf RM, Swedberg K, Schwartz P, Bigger Jr JT, *et al* — Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA* 2002; **288:** 701-9.

7 Gan Y, Gong Y, Tong X, Sun H, Cong Y, Dong X, Wang Y, Xu X, Yin X, Deng J, Li L — Depression and the risk of coronary heart disease: a meta-analysis of prospective cohort studies. *BMC Psychiatry* 2014; **14:** 371.

8 Wu Q, Kling JM. Depression and the risk of myocardial infarction and coronary death: a meta-analysis of prospective cohort studies. *Medicine* 2016; 95.

9 Dempe C, Jünger J, Hoppe S, Katzenberger ML, Möltner A, Ladwig KH, Herzog W, Schultz JH — Association of anxious and depressive symptoms with medication nonadherence in patients with stable coronary artery disease. Journal of Psychosomatic Research 2013; **74:** 122-7.

10 Bauer LK, Caro MA, Beach SR, Mastromauro CA, Lenihan E, Januzzi JL, *et al* — Effects of depression and anxiety improvement on adherence to medication and health behaviors in recently hospitalized cardiac patients. *The American Journal of Cardiology* 2012; **109:** 1266-71.

11 Davidson KW, Rieckmann N, Clemow L, Schwartz JE, Shimbo D, Medina V, Albanese G, Kronish I, Hegel M, Burg MM — Enhanced depression care for patients with acute coronary syndrome and persistent depressive symptoms: coronary psychosocial evaluation studies randomized controlled trial. *Archives of Internal Medicine* 2010; **170:** 600-8.

12 Huffman JC, Mastromauro CA, Sowden G, Fricchione GL, Healy BC, Januzzi JL — Impact of a depression care management program for hospitalized cardiac patients. Circulation: *Cardiovascular Quality and Outcomes* 2011; **4:** 198-205.

13 Whooley MA — Depression and cardiovascular disease: healing the broken-hearted. *JAMA* 2006; **295:** 2874-81.

14 Kim JM, Stewart R, Lee YS, Lee HJ, Kim MC, Kim JW, Kang HJ, Bae KY, Kim SW, Shin IS, Hong YJ — Effect of Escitalopram vs Placebo Treatment for Depression on Long-term Cardiac Outcomes in Patients With Acute Coronary Syndrome: A Randomized Clinical Trial. *JAMA* 2018; **320:** 350-8.

15 Berkman LF, Blumenthal J, Burg M, Carney RM, Catellier D, Cowan MJ, Czajkowski SM, DeBusk R, Hosking J, Jaffee A, Kaufmann PG — Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. *JAMA* 2003.

Review Article

Takayasu's arteritis : role of imaging

Rabindra Nath Chakraborty[1], Arindam Pande[2], Soumya Patra[3], Sumanto Mukhopadhyay[4], Tanmoy Bandyopadhyay[5]

Takayasu arteritis (TA) is a chronic large vessel vasculitis that affects aorta, its main branches and pulmonary arteries. The inflammatory process results in stenosis, occlusion, dilation or aneurysm formation in the arterial wall. TA has been described in different parts of the world and affects predominantly young individuals (<50 years of age). Patients with TA may present constitutional symptoms, vascular pain (e.g. carotidynia) and typical features such as limb claudication, decreased or absent peripheral pulses, vascular bruits, hypertension, and reduction or discrepancies in blood pressure between arms. A proper diagnosis of TA is an important issue since delays may result in significant morbidity. The definition of TA was included in the 1994 and 2012 Chapel Hill Consensus Conference and TA was categorized as a large vessel vasculitis. The first diagnostic criteria for TA were developed by Ishikawa in 1988 and modified by Sharma et al., in 1995. Different imaging modalities play a very vital role in the management of TA. Some of the modalities are useful in early diagnosis; some are helpful for monitoring disease activity and planning management. Current article aims at briefly discussing the role of different imaging modalities in TA.

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***Key words* : Takayasu arteritis , Imaging, X-Ray, FDG-PET, USG, CT, MRI.**

The first description of TA is usually attributed to Mikito Takayasu who presented a case of a 21 year-old woman with arteriovenous anastomosis surrounding the papilla on the eyeground in the 12th Annual Meeting of the Japan Ophthalmology Society in 1905. After Mikito Takayasu, the first reports of TA in medical literature in English were published in the early 1950s and in both publications TA was referred as "pulseless disease".

Takayasu arteritis (TA) is a chronic granulomatous large vessel vasculitis that affects the aorta, its main branches and pulmonary arteries[1]. The inflammatory process initially leads to thickening of the arterial wall and may result in stenosis, occlusion, dilatation or aneurysm formation. At disease presentation or during relapses, TA patients may present non-specific inflammatory complaints such as fever, malaise, anorexia, weight loss, myalgia or arthralgias which can be associated with vascular pain (eg carotidynia). As arterial lesions ensue, more characteristic features of TA may be found such as limb claudication, decreased or absent peripheral pulses, vascular bruits, hypertension, and reduction or discrepancies in blood pressure due to stenotic or occlusive lesions between arms. Heart failure may develop as a consequence of hypertension, coronary heart disease and/or aortic regurgitation. Transient ischemic attacks, stroke and mesenteric ischemia are other ischemic manifestations of TA. The vast majority of arterial lesions in TA are stenotic whereas aneurysms can be found in up to one third of TA patients[2]. Although geographical differences regarding the distribution of arterial lesions have been described in TA, the aorta is the most affected artery followed by subclavian, common carotid and renal arteries[3].

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Imaging in Takayasu's Arteritis :

In early-phase Takayasu arteritis, Computed Tomography (CT) and Magnetic Resonance (MR) imaging show thickening of the aortic wall. In late-phase Takayasu arteritis, angiography usually demonstrates luminal changes such as stenosis, occlusion, or aneurismal dilatation of the aorta and pulmonary artery and their branches[4,5]. However, absence of such luminal changes does not exclude the possibility of early-phase Takayasu arteritis. Familiarity with the varied chest radiographic, angiographic, CT, and MR Imaging features of Takayasu airteritis will permit earlier diagnosis and treatment.

Chest Radiographic Features :

The Chest radiographic manifestations include loss of sharp definition and a wavy or scalloped appearance of the descending thoracic aorta (Fig 1)[6]. Hayashi *et al*[7] reported that hilar enlargement, although rare, may be a new radio graphic finding in early-phase Takayasu Artentis (Fig 2). Such subtle findings in a young female patient should alert the radiologist to the diagnosis of early-phase Takayasu arteritis.

Ultrasonography :

Duplex Doppler ultrasonography (US) may be used to identify circumferential vessel wall thickening and thereby evaluate and monitor disease in the aorta and branch vessels (Fig 3). Sonography of carotids and subclavian arteries aids in detection of TA at an early stage, where characteristic long segment involvement with homogenous, midechoic, circumferential arterial wall thickening, which has been described as the "Macaroni's sign" may be found.[8] However, the examination is operator dependent and also depends on a suitable acoustic window. Furthermore, it has a low negative predictive value.

Angiographic Features :

Aortography may not show any intraluminal changes because the basic pathologic features of early-phase Takayasu Arteritis are mural changes in the great vessels[9]. On aortograms, the thickness of the wall of the descending thoracic aorta is measured as the distance between the intraluminal contrast medium and the air in the lung. This Measurement includes, the thickness of the two pleural layers (which may be negligible) and possibly the thickness should of periaortic infiltration. However, the thickness of the wall of the pulmonary artery is difficult to measure on angiograms.

Rarely, when the inflammatory changes are severe, granulomatous or diffuse productive in flammation in the media and adventitia is associated with marked secondary intimal hyperplasia, resulting in stenosis of the aortic lumen (Fig 4). Coronary involvement in TA is best delineated in conventional coronary angiography[10].

CT and MRI :

By demonstrating arterial wall changes, cross sectional imaging techniques such as CT and MR Imaging play an important role in early diagnosis of Takayasu artentis. The significant feature of early-phase Takayasu Artentis is aortic wall thickening.

Hayashi *et al* reported that a double ring pattern at enhanced CT is useful for early diagnosis of early-phase Takayasu Arteritis and evaluation of the effects of steroid therapy[7]. On unenhanced CT scans, the vascular wall is clearly distinguished from the vascular lumen by attenuation similar to or higher than that of muscle. On Enhanced CT scans, the wall shows the double ring pattern: a poorly enhanced in side ring and a well-enhanced outside ring (Fig 5). The inside ring is considered to represent mucoid or gelatinous swelling of the intima; the outside ring is considered to represent active medial and adventitial inflammatory Verse change.

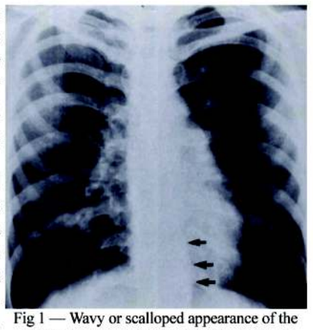

Fig 1 — Wavy or scalloped appearance of the descending thoracic aorta in chest radiograph

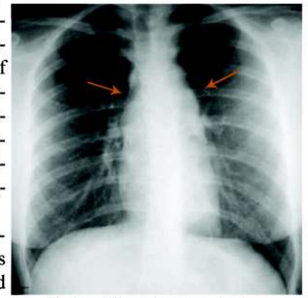

Fig 2 — Hilar enlargement in chest radiograph in a young female patient of Takayasu arteritis

The Inflamed arterial wall enhances at contrast-enhanced CT, because adventitial vascular structures in the aortic wall are probably enlarged vasa vasorum. In all 10 Healthy adults studied by Park et al, transverse arterial-phase spiral CT angiograms showed an aortic wall that was less than 1 mm thick or even imperceptible; the aortic wall could not be identified on precontrast and delayed images. Therefore, the sensitivity and specificity of CT for the detection of significant arterial wall thickening are thought

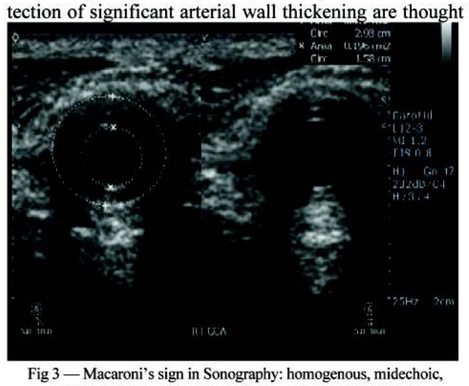

Fig 3 — Macaroni's sign in Sonography: homogenous, midechoic, circumferential arterial wall thickening in Takayasu arteritis

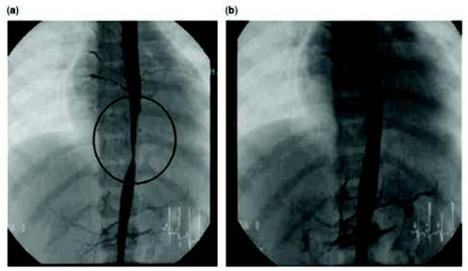

Fig 4 — Diffuse stenosis of abdominal aorta before (a) and after (b) stent angioplasty in a patient of Takayasu arteritis

Fig 5 — Double ring pattern in CT Angiography: a poorly enhanced in side ring and a well-enhanced outside ring in a patient of Takayasu arteritis

to be high (Fig 5).

Arterial wall thickening can also be demonstrated with MR Imaging (Fig 6). MR imaging has the advantages of direct imaging in the axial, sagittal, and coronal planes with good contrast resolution, and the spin-echo technique allows differentiation of the arterial lumen from its wall without contrast medium[11]. An Imaging section perpendicular to the vessel of interest is best suited for assessing wall thickness with MR imaging. MR imaging in particular allows better soft-tissue differentiation and can show other signs of inflammation, including mural edema and increased mural vascularity. Other advantages of MR imaging are the lack of iodinated contrast material or ionizing radiation.

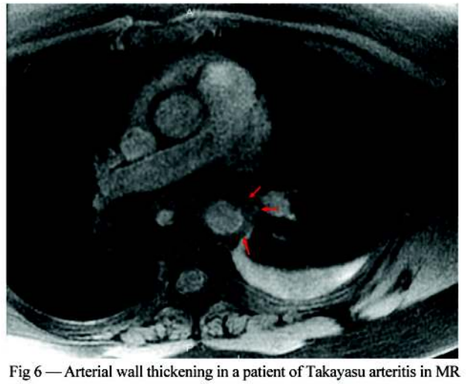

Fig 6 — Arterial wall thickening in a patient of Takayasu arteritis in MR Imaging

During the course of early-phase Takayasu Arteritis, either spontaneously or with steroid therapy, the aortic wall thickening may be reduced, corresponding to a decrease in active inflammation in and around the aortic wall. Steroid therapy has resulted in a dramatic improvement in clinical and radiologic abnormalities in patients with early-phase Takayasu Arteritis. Hayashi et al reported the first case of early-phase Takayasu Arteritis in which reduction of aortic wall thickening after steroid therapy was documented with CT[7]. Follow-up MR imaging of patients with early-phase Takayasu arteritis demonstrated significant reduction of wall thickening in the aorta and pulmonary artery after steroid therapy.

FDG-PET Scanning :

18F-fluorodeoxyglucose–positron emission tomography or FDG-PET scanning has been proposed as a new way of assessing disease activity in Takayasu arteritis (TA)[12]. This is a noninvasive metabolic imaging modality based on the regional distribution of 18F-fluorodeoxyglucose, which accumulates in hypermetabolic cells. Some authors have suggested that it could play a role in the management of large-vessel vasculitis because of its capacity to detect areas of increased glucose metabolism present in the vascular wall. Preliminary studies have shown that FDG-PET scanning had a sensitivity and specificity of 92% and 100%, respectively, for the assessment of active TA.

Conclusion :

Both conventional and modern imaging modalities play very vital role in the management of TA. These include early diagnosis, planning therapy, monitoring disease activity and also follow up of patients. Proper selection of imaging modalities as well as good interdepartmental coordination between rheumatologist, radiologist, physician and cardiologist is quintessential in formulating a perfect management plan.

References

1 Kerr GS, Hallahan CW, Giordano J, Leavitt RY, Fauci AS, Rottem M, *et al* — Takayasu arteritis. *Ann Intern Med* 1994; **120:** 919e29.

2 Maksimowicz-McKinnon K, Clark TM, Hoffman GS — Limitations of therapy and a guarded prognosis in an American cohort of Takayasu arteritis patients. *Arthritis Rheum* 2007; **56:** 1000e9.

3 Johnston SL, Lock RJ, Gompels MM — Takayasu arteritis: a review. *J Clin Pathol* 2002; **55:** 481e6.

4 Mason JC — Takayasu arteritise advances in diagnosis and management. *Nat Rev Rheumatol* 2010; **6:** 406e15.

5 Freitas DS, Camargo CZ, Mariz HA, Arraes AE, de Souza AW — Takayasu arteritis: assessment of response to medical therapy based on clinical activity criteria and imaging techniques. *Rheumatol Int* 2012; **32:** 703e9.

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Review Article

Angiotensin receptor / neprilysin inhibitors (ARNIs) : the new hope in the management of heart failure

Soumya Patra[1], Rabin Chakraborty[2]

Heart failure (HF) represents major challenges in cardiovascular disease and despite newer therapeutic advances, mortality still remains high. Inhibition of neurohumoural pathways such as the renin angiotensin aldosterone and sympathetic nervous systems is central in the management of heart failure. LCZ696 (sacubutril/valsartan), a first-in-class angiotensin II AT1 receptor neprilysin inhibitor (ARNI), has a unique mode of action that targets both pathways. The Prospective comparison of ARNI with angiotensin convertase enzyme inhibitor (ACEI) to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF) trial demonstrated that morbidity and mortality can be improved with the ARNI. This trial suggests that sacubitril/valsartan should replace an ACE inhibitor or angiotensin receptor blocker for the treatment of symptomatic patients (NYHA II–IV) with HF with reduced ejection fraction. This review will explore the background of neprilysin inhibition in management of HF, the results of the PARADIGM-HF trial and also guide how to use sacubitril/valsartan in clinical practice.

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***Key words* : ARNI, Heart Failure, sacubatril/valsartan.**

Heart failure (HF) is defined as a complex clinicalsyndrome, and can result from any structural or functionalcardiac disorders which impair the ability of ventriclesto fill with or eject blood[1]. The renin angiotensin aldosterone system (RAAS)system is main contributing agent in the pathophysiology ofHF and its modulation is central to modify the disease process in HF with reducedejection fraction (HFrEF)[2]. Successive randomisedcontrolled trials (RCT) have proved that blockadeof RAAS improves morbidity and mortality inpatients with HFrEF[3]. Though the prognosis ofHFrEF has been improved over the years, still there is high mortality and morbidity as it remains a complexsyndrome involving a various neurohormonalpathways[4]. Therefore, further therapies need to develop to improveoutcomes in these patients.

The Natriuretic Peptide System :

The natriuretic peptide system counter regulates those detrimental effects of the upregulation of RAAS that occurs in HFrEF. It inhibits secretion of arginine vasopressin and modulates the autonomic nervous system in the favour of our body[5].

Sodium and water retention and vasoconstriction caused by activation of RAAS and the sympathetic nervous system, and the action of vasopressin, lead to increased ventricular preload and afterload and elevated wall stress which leads to production of pre-pro B-type natriuretic peptide (BNP) which is cleaved to BNP and N-terminal proBNP (NT-proBNP)[6]. The BNP acts to promote natriuresis and vasodilation. Whereas, atrial stretch leads to the production of pre-proatrial or A-type natriuretic peptide and ultimately atrial natriuretic peptide (ANP) which also has similar biological properties to BNP. 6C-type natriuretic peptide (CNP) is released from endothelial cells and acts in a paracrine fashion but is only found in low concentrations in circulating blood[6]. Though Nesiritide, a recombinant human BNP, initially showed promising beneficial effects on haemodynamics and natriuresis in patients with HFrEF, but it failed in to improve outcomes in large-scale randomised controlled trial[7]. So another strategy was to inhibit the breakdown of natriuretic peptides by inhibiting a membrane bound endopeptidase, neprilysin[8]. Neprilysin is found in a number of tissues but in especially high concentrations in the kidney. Initial Neprilysin Inhibitors like oral (racecodotril) and intravenous (candoxatrilat) formulation were successful in promoting natriuresis and increasing urinary excretion of ANP but failed to show any clinical benefits in HFrEF[9].

Dual Neprilysin and ACE Inhibition :

Dual blockade of RAAS and the natriuretic peptide system came as a solution to the problem of lone neprilysin inhibition. The combined ACE and neprilysin inhibitor omapatrilat was studied in a large randomised controlled trial against enalapril 10 mg twice daily in the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) trial. Omapatrilat failed to reduce primary end point (death from any cause or HF hospitalisations). The rate of angio-oedema was much higher in the omapatrilat group as both ACE and neprilysin break down bradykinin and omapatrilat also inhibits aminopeptidase P which also catabolises bradykinin. Therefore, unintended excessive potentiation of bradykinin and resultant high rates of serious angio-oedema led to the discontinuation of the clinical development of this drug.10

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Angiotensin Receptor Blocker and Neprilysin Inhibitors :

Combining an angiotensin receptor blocker (ARB) and a neprilysin inhibitor was the next logical step and potential solution to the problem encountered with omapatrilat. The angiotensin receptor neprilysin inhibitor (ARNI) sacubitril/valsartan (formerly known as LCZ696) was designed with the aim of inhibiting neprilysin while blocking the adverse effects of RAAS and reducing bradykinin potentiation.The drug LCZ696 is made of the ARB valsartan and neprilysin inhibitor prodrug sacubitril. As the active metabolite of sacubitril, sacubitrilat (LBQ657) does not inhibit aminopeptidase P, the risk of angio-oedema was expected to be lower than with omapatrilat. The systemic exposure delivered by sacubitril/valsartan 97 mg/103 mg (200 mg LCZ696) is equivalent to 160 mg of valsartan and neprilysin is almost completely inhibited for up to 12 h. The Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF) was conducted to test whether 97 mg/103 mg twice daily of sacubitril/valsartan was superior to enalapril 10 mg twice daily in reducing the primary end point of CV death or HF hospitalisation.The trial was terminated early, on the recommendation of the Data Monitoring Committee, due to a sustained and highly significant reduction in the risk of the primary composite end point (CV death or HF hospitalisation) and in CV mortality in the sacubitril/valsartan group compared with the enalapril group. At the end of the trial, there was a 20% relative risk reduction in the primary end point as well as a 16% reduction in all-cause mortality. The two major modes of CV death, sudden death and death from worsening HF were equally and significantly reduced.Both first hospitalisations for HF and total (including repeat) hospitalisations were also reduced by 21% and 23%, respectively. Therefore, for every 1000 patients switched from enalapril to sacubitril/valsartan, over a median of 27 months, there would be: 47 less primary end points (CV death or HF hospitalisations), 33 less CV deaths, 28 less first hospitalisations for HF (53 less total hospitalisations for HF) and 32 less deaths from any cause.No interactions were observed between any of the subgroups and study outcomes.There was no statistically significant difference in the rate of angio-oedema with sacubitril/valsartan although numerically more cases were observed than in the enalapril group. Hypotension was significantly more common with sacubitril/valsartan than with enalapril (14% *versus* 9% in the in the sacubitril/valsartan and enalapril groups respectively, $p<0.001$), although this rarely led to study drug discontinuation (0.9% and 0.7% in the sacubitril/valsartan and enalapril groups respectively, $p=0.38$). Conversely, renal dysfunction, hyperkalaemia and cough were less common with sacubitril/valsartan than with enalapril. Subsequent analyses of PARADIGM-HF have confirmed that the relative reductions in morbidity and mortality and differential rates of adverse events were similar across all agesand baseline risk of death as determined by risk-scoring systems[11-14].

With the result of PARADIGM-HF trial, both American College of Cardiology and European Society of Cardiology included ARNI as class IB recommendation of using it in HFrEF. It can be used either as de novo or in place of ACEI/ ARB.

How should ARNI be Prescribed ?

ARNI should not be given in conjunction with another ARB or renin inhibitor (because of the risk of renal impairment and hyperkalaemia) or an ACE inhibitor (risk of renal impairment, hyperkalaemia and angio-oedema). Due to the potential risk of angio-oedema when used concurrently with an ACE inhibitor, sacubitril/valsartan must not be started for at least 36 h after discontinuing an ACE inhibitor.15The starting dose of sacubitril/valsartan is 49 mg/51 mg twice daily. The dose should be doubled every 2–4 weeks as tolerated by the patient to the maximum dose of 97 mg/103 mg twice daily. Patients should also be prescribed other evidence-based drugs (ß-blocker, mineralocorticoid receptor antagonist, ivabradine and digoxin) and devices (cardiac resynchronisation therapy (CRT), implantable cardioverter defibrillator (ICD)), as appropriate.

Side Effects and Cautions :

Renal function, potassium and blood pressure should be monitored as for any other RAAS blocker. The drug is not started in those with a systolic blood pressure of <100 mm Hg. In the event of the development of hypotension, renal impairment or hyperkalaemia, evaluation of the potential causes should be searched and appropriate measures like reducing the dose of other non-essential blood pressure-lowering drugs, adjusting the dose of diuretics, discontinuing other drugs such as non-steroidal anti-in-

flammatory drugs must be done. The development of angio-oedema should lead to immediate discontinuation and treatment with appropriate therapy until it has resolved. Rates of discontinuation for renal impairment were lower in the sacubitril/valsartan group compared with the enalapril group (0.7% vs 1.4% respectively, p=0.002). As sacubitril/valsartan increases levels of circulating BNP therefore BNP is not useful for monitoring the prognosis of these patients.16NT-proBNP still be used as a marker for HF.

Heart Failure with Preserved Ejection Fraction (HFpEF) :

Currently there is also experience with sacubitril/valsartan in HFpEF. In the Prospective comparison of ARNI with ARB on Management Of heart failure with preserved ejectioN fracTion (PARAMOUNT) trial, 301 patients with HF-PEF were randomised to valsartan or sacubitril/ valsartan.17NT-proBNP fell in the latter group along with reductions in NYHA class and left atrial volumes. On the basis of these findings and the favourable effects seen in PARADIGM-HF a large multicentre randomised outcomes trial of sacubitril/valsartan versus valsartan, PARAGON-HF, is currently recruiting.

Summary :

With the result of PARADIGM-HF, ARNI brings new era of hope in the management of HFrEF. ARNI should replace ACE inhibitor/ ARB in all symptomatic patients with HF as it reduces mortality, morbidity and repeat HF admission more than the age old drugs. It is also reflected in the latest HF guidelines. Still we need more data before prescribing in HFpEF.

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Conflict of Interest : None.

References

1 Yancy CW, Jessup M, Bozkurt B — ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am CollCardiol* 2013; **62:** e147–239.

2 McMurray JJ, Adamopoulos S, Anker SD — ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *Eur Heart J* 2012; **33:** 1787-847.

3 Cohn JN, Tognoni G — A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001; **345:** 1667-75.

4 Jhund PS, MacIntyre K, Simpson CR — Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: a population study of 5.1 million people. *Circulation* 2009; 119: 515-23.

5 Daniels LB, Maisel AS — Natriuretic peptides. *J Am Coll Cardiol* 2007; **50:** 2357-68.

6 Schulz-Knappe P, Forssmann K, Herbst F — Isolation and structural analysis of "urodilatin", a new peptide of the cardiodilatin-(ANP)-family, extracted from human urine. *Klin Wochenschr* 1988; **66:** 752-9.

7 O'Connor CM, Starling RC, Hernandez AF — Effect of nesiritide in patients with acute decompensated heart failure. *N Engl J Med* 2011; **365:** 32-43.

8 Hata N, Seino Y, Tsutamoto T — Effects of carperitide on the long-term prognosis of patients with acute decompensated chronic heart failure: the PROTECT multicenter randomized controlled study. *Circ J* 2008; **72:** 1787-93.

9 Bevan EG, Connell JMC, Doyle J — Candoxatril, a neutral endopeptidase inhibitor: efficacy and tolerability in essential hypertension. *J Hypertens* 1992; **10:** 607-13.

10 Packer M, Califf RM, Konstam MA — Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). *Circulation* 2002; **106:** 920-6.

11 Ruilope LM, Dukat A, Böhm M — Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. *Lancet* 2010; **375:** 1255–66.

12 McMurray JJV, Packer M, Desai AS — on behalf of the PARADIGM-HF Committees, Investigators. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact. *Eur J Heart Fail* 2013; **15:** 1062-73.

13 McMurray JJV, Packer M, Desai AS —. Baseline characteristics and treatment of patients in prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial (PARADIGM-HF). *Eur J Heart Fail* 2014; **16:** 817-25.

14 Jhund PS, Fu M, Bayram E — PARADIGM-HF Investigators and Committees. Efficacy and safety of LCZ696 (sacubitril-valsartan) according to age: insights from PARADIGM-HF. *Eur Heart J* 2015; **36:** 2576-84.

15 Simpson J, Jhund PS, Silva Cardoso J — Effect of LCZ696, compared with enalapril, according to baseline risk in the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). *J Am Coll Cardiol* 2015; **66:** 2059-71.

16 US Food and Drug Administration. ENTRESTO (sacubitril and valsartan). Highlights of prescribing information. (cited 30 September 2015). http://www.accessdata.fda. gov/drugsatfda_docs/label/2015/207620Orig1s000lbl.pdf

17 Solomon SD, Zile M, Pieske B — The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet* 2012; **380:** 1387-95.

Case Report

NIH catheter induced RV perforation in a patient of tetralogy of fallot

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Using a side-hole catheter for RV angiogram is a standard protocol. Perforation of RV during this procedure caused by the power of injection is a very rare complication and not well reported in literature. Here we are reporting a case of free wall perforation during RV angiogram induced by a NIH catheter. A 5 year girl (10 kg) with a diagnosis of tetralogy of fallot was planned for preoperative cath study. RV was catheterized with a 5F NIH catheter (Cordis, Cashel, Ireland) with 4 side-holes. Angiogram was obtained with Iohexol contrast (15 ml, at 10 ml / second, 700 psi pressure limit). Immediately after the injection there was a perforation of RV free wall with resultant spillage of blood and contrast into pericardial cavity. The baby became hemodynamically unstable and ultimately developed cardiac arrest. Probably one of the side holes lied firmly against the endocardium. We started cardiopulmonary resuscitation, withdrawn the catheter, reversed the heparin with protamine sulfate introduced a 5 F sheath into pericardial cavity and 90 ml of blood was evacuated. After the pericardiocentesis the baby's hemodynamic parameters started improving gradually. We kept the pericardial sheath overnight and there were no further complications. In tetralogy of fallot, generally the RV is very much hypertrophied. Encountering a perforation of RV free wall by a side-hole angiography catheter is an extremely unusual circumstance.

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***Key words* : NIH catheter, TOF, RV perforation.**

In the era of interventional cardiology, catheter-based diagnostic and therapeutic procedures are rapidly advancing. However, catheter related complications are still there[1]. It occurs more frequently with debulking devices and often as a consequence of guide wire migration and injury[2]. Acute hemorrhagic pericardial collection secondary to iatrogenic inadvertent cardiac perforation often leads to fatal tamponade. Echo-guided pericardiocentesis has been shown to be effective and primary management[3]. In tetralogy of fallot (TOF), the RV is hypertrophied. Using a side-hole catheter for RV angiogram is a standard protocol. Perforation of RV of patient of TOF during this procedure caused by the power of injection is a very rare complication and not well reported in literature. Here we are reporting a case of free wall perforation during RV angiogram induced by a NIH catheter.

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Case Report

A 5-year-old baby weighing 10 kg, having Tetralogy of Fallot, was posted for preoperative diagnostic catheterization study. On examination, there was central cyanosis, grade IV clubbing, pulse rate 110/min, NIBP 90/60mmHg, ejection systolic murmur over pulmonary area. In chest X ray, there was cardiomegaly and boot shaped heart with oligemic lung fields. SpO_2 in room air was 86%.

In the catheterization laboratory, intravenous cannula was put after prior application of prilox patch. Premedication was given with glycopyrrolate (0.1mg), fentanyl (20mcg), and midazolam (1mg) intravenously 5 minutes before induction. Induction was done with sevoflurane (6%) and LMA (size 2) was inserted. Patient was kept in spontaneous ventilation. Local infiltration with 1% lignocaine was given and femoral artery and femoral vein were cannulated. A 5F NIH catheter (Cordis, Cashel, Ireland) with 4 side-holes was inserted to RV. At that time, ECG showed different types of ill-sustained arrhythmia, although blood pressure was stable. Angiogram was obtained with Iohexol contrast (15 ml, at 10 ml / second, 700 psi pressure limit). Immediately after the injection there was a perforation of RV free wall with resultant spillage of blood and contrast into pericardial cavity (Fig 1). Probably one of the side holes lied firmly against the endocardium. Gradually the contrast material was evenly distributed within the pericardial sac (Fig 2). NIBP suddenly dropped to 40/30mmHg and heart rate decreased (50/min). Inj atropine (0.2mg) was administered immediately and patient was resuscitated with intravenous fluids. We withdrawn the catheter, reversed the heparin with protamine sulfate and waited for few minutes prior to any further intervention. But, unfortunately,

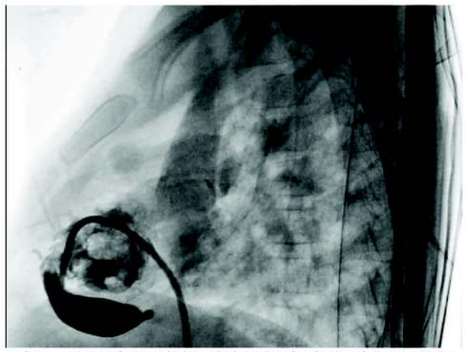

Fig 1 — RV angiogram in lateral view showing both pulmonary artery (confluent) and ascending aorta with overriding. It is also showing the RV perforation and leakage of blood with contrast material into pericardial cavity

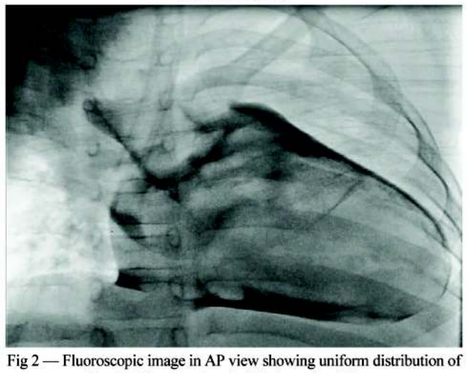

Fig 2 — Fluoroscopic image in AP view showing uniform distribution of blood with contrast material into pericardial sac

the arrhythmia continued and ultimately the patient developed cardiac arrest. Patient was intubated immediately and cardiopulmonary resuscitation (CPR) was started. Transthoracic echocardiography showed features of cardiac tamponade. Urgent pericardiocentesis through sub-xiphoid access was performed and 90mL of blood was aspirated. Fortunately, heart started to contract again, but hypotension still persists for some time. Later 1 unit packed cell transfusion was started and patient's vitals were improved gradually. We kept the pericardial sheath (Fig 3) overnight and there were no further complications.

Discussion

Tetralogy of Fallot is a cardiac anomaly that refers to a combination of four related cardiac defects that commonly occur together.The four defects are ventricular septal defect, overriding of aorta, right ventricular outflow tract obstruction, and right ventricular hypertrophy. In 2%-14% of patients with TOF, there are associated coronary artery anomalies[4]. Diagnostic catheterization study before surgical correction is a usual procedure but is not free from complication. Cardiac perforation is a rare but life-threatening complication of catheterization. The incidence of cardiac perforation has been reported to be 1.5% to 4.7% for valvuloplasty[5,6], 0.2% to 1% for radiofrequency ablation[7,8], 0.1% to 0.2% for electrophysiologic study[9], 0.5% for cardiac biopsy[10], 0.03% for coronary angioplasty[11], and 0.01% for diagnostic catheterization[5].

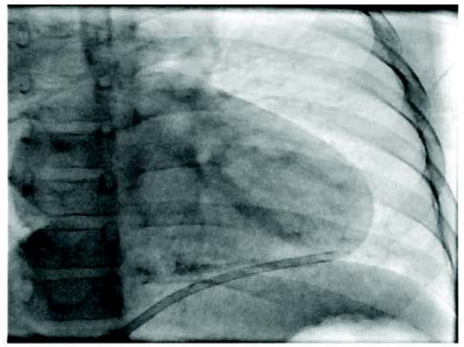

Fig 3 — Fluoroscopic image in AP view showing successful pericardiocentesis with in-situ pericardial sheath

In tetralogy of fallot, generally the RV is very much hypertrophied. Encountering a perforation of RV free wall by a side-hole angiography catheter is an extremely unusual circumstance. NIH catheter is also considered a very safe option for any diagnostic procedure as it has 4 side-holes only. In our case probably one of the side holes lied firmly against the endocardium which created the inadvertent perforation of thick RV wall. Paediatric patient has less cardiopulmonary reserve; moreover, small amount of acute collection can cause the tamponade to impair the contraction of the heart and cardiac output. The only aim of management is releasing the tamponade effect. In our case however coordinated team approach by cardiac anaesthetists and the whole cathlab team led to early diagnosis of the fatal rare complication and step-wise management. As an end result patient was saved in spite of having a cardiac arrest.

References

1 V Stolt, S Cook, L R¨aber — Amplatzer septal occlude to treat iatrogenic cardiac perforations. *Catheterization and Cardiovascular Interventions* 2012; **79:** 263-70.

2 Witzke CF, Martin-Herrero F, Clarke SC, Pomerantzev E, Palacios IF — Thechanging pattern of coronary perforation during percutaneous coronary intervention in the New Device Era. *Journal of Invasive Cardiology* 2004; **16:** 257-301.

3 Vaitkus PT, Herrmann HC, LeWinter MM — Treatment of malignant pericardial effusion. *Journal of the American Medical Association* 1994; **272:** 59-64.

4 Mawson JB — Congenital heart defects and coronary anatomy. *Texas Heart Institute Journal* 2002; **29:** 279-89.

5 Friedrich SP, Berman AD, Baim DS, Diver DJ — Myocardial perforation in the cardiac catheterization laboratory: incidence, presentation, diagnosis, and management. *Catheterization and Cardiovascular Diagnosis* 1994; **32:** 99-107.

6 Isner JM — Acute catastrophic complications of balloon aortic valvuloplasty. Journal of the American College of Cardiology 1991; **17:** 1436-44.

7 "Le Groupe de Rythmologie de la Societe Franc, aise de Cardiologie. Complications of radiofrequency ablation: a French experience," Archives des Maladies du Coeur et des

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Case Report

Calcified coronary artery disease — CABG or PCI

Sumanto Mukhopadhyay[1], Pooja Banerjee[2], Soumya Patra[3], Arindam Pande[4], Rabindra Nath Chakraborty[5]

Coronary artery calcification (CAC) is highly prevalent in patients with coronary artery disease (CAD) and is associated with major adverse cardiovascular events. Heavily calcified coronary diseases remain a formidable challenge for percutaneous interventions (PCI). This article highlights the use of Rotational Atherectomy as a primary strategy for treating calcified lesions in order to facilitate optimal stent delivery and expansion as well as the importance of SYNTAX 2 score for determing the optimal strategy of either PCI or Coronary artery bypass surgery (CABG) as treatment modality.

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Key words **: PCI, Rotablation, Calcified coronary arteries.**

Multi vessel calcified coronary artery disease is one of the commonest causes of referral for coronary artery bypass surgery. But the advent of rotablation has changed the paradigm of treatment. Here we report a case of multi vessel calcified coronary artery disease which was successfully managed with percutaneous coronary intervention (PCI) and rotablation.

Case Report

A 79 years old male, known case of hypertension and chronic obstructive pulmonary disease presented with post infarction angina following an inferior wall myocardial infarction (MI). Routine examination was unremarkable except for presence of bibasal crepitations and diffuse rhonchi. ECG revealed evolved inferior wall MI and there was hypokinesia of basal segment on echocardiogram with an ejection fraction of 45%. Coronary angiography revealed 90% stenosis in mid part of the right coronary artery (RCA) with significant calcification and critical stenosis in the proximal to mid part of the left anterior descending artery (LAD) with severe calcification and discrete 90% stenosis in the distal LAD.

A heart team approach was take and the patient was deemed as a high risk case for coronary artery bypass surgery (CABG). Predicted 4 year mortality as per Syntax 2 score in this case was 17.6% with PCI *versus* 34.5% with CABG. Syntax score was 23. After discussion with the patient and family, angioplasty was planned after obtaining proper informed consent.

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PCI was done through right femoral approach. 6F JR 3.5 guide catheter was used to engage the right coronary artery (RCA). Initially sion blue wire was used to cross the lesion and attempts of pre-dilations were made but it was impossible to cross even with an 1.5 mm balloon due to the severe calcification. Hence, a rotablation was considered and rota wire was used to recross the lesion. We used the Rotalink plus system, (Boston Scientific Corporation, USA), with the exchange-length rotablator floppy wire. Rotational burr speed was set between 160000 to 180000 revolutions per minute (RPM). Additionally, a pressurised saline solution containing verapamil 5 mg/500 ml, nitroglycerine 2mg/500 ml and heparin 5000 IU/500 ml were used for continuous flushing of the rotablator system to prevent thrombosis, cooling and coronary spasm. Rotablation was done with 1.5 mm bar Rotalink Plus. Asahi Sion Blue guide wire was used to recross the lesion. Sequential pre-dilatations were done with semi-compliant (SC) balloons. An Everolimus eluting stent 4.0 x 32 mm was deployed in proximal-mid RCA. Stent boost guided post dilatation was done with NC balloon 4.0 x 8. Post procedure TIMI III flow was achieved in RCA.

6F CLS 3.5 guide catheter was used to engage the left coronary artery. Initially Rota wire placed to distal LAD. Rotablation was done to proximal LAD with 1.5 mm bar Rotalink Plus. Pre dilatation was done with 2.75 x 12 balloon. An everolimus eluting 4.0 x 37 mm stent was deployed in proximal LAD at 10 atm. Stent boost guided post dilatation was done with NC balloon 4.0 x 8.0mm. Another Everolimus eluting stent 3.0 x 16 mm stent was deployed in distal LAD. Post procedure TIMI III flow was achieved in LAD. A total of 14000 units of unfractionated heparin was used. Patient was discharged in stable condition and is doing well on follow up.

Discussion

This article highlights the importance of heart team approach and Syntax 2 score[1] which takes into account additional clinical parameters, apart from the coronary anatomy (Syntax score)[2] in deciding PCI *versus* CABG. Also, in CABG it is difficult to anastomose the grafts on the calcified native arteries. Thus, PCI with debulking or plaque modifying strategies can definitely provide better outcomes.

Rotational atherectomy is used as a lesion preparation and plaque modification tool in severely calcified coronary arteries prior to stent implantation[3,4,5]. Debulking complex atherosclerotic lesions and plaque modification prior to stenting results in better luminal gain with less late luminal loss[6]. The success of the intervention depends on the rotablation technique (burr-to-artery ratio, RPM) and operators' experience[7,8]. Complications include coronary artery dissection (risk 6-8%), perforation (risk 0-1.5%), slow-flow phenomenon (risk 1.2-7.6%), severe spasm (risk 1.6-6.6%) or abrupt vessel closure (risk 1.8-11.2%), and emergency CABG (risk 1.0-2.5%)[9]. Fundamental elements of optimal technique include use of a single burr with burr-to-artery ratio of at least 0.5 to 0.6-rotational speed of 140,000 to 150,000 RPM. Optimal antiplatelet therapy, vasodilators, flush solution, and provisional use of atropine, temporary pacing, vasopressors, and mechanical support may prevent slow-flow/no-flow. In a comparative study of rotational atherectomy with CABG for patients with failed PCI, there was no significant difference in major cardiovascular events but rotational atherectomy carried a lower risk of periprocedural complications and a higher rate of target vessel revascularisation[10].

Rotablation produces lumen enlargement by physical removal of plaque and reduction in plaque rigidity, facilitating dilation. It ablates plaque using a diamond-encrusted elliptical burr, rotated at high speeds (140,000 to 180,000 RPM) by a helical driveshaft, that advances gradually across a lesion over a guidewire. The burr preferentially ablates hard, inelastic material, such as calcified plaque,

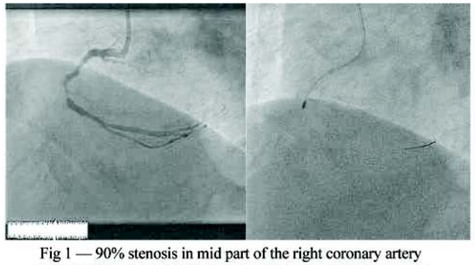

Fig 1 — 90% stenosis in mid part of the right coronary artery with significant calcification. Rotablation with 1.5 mm burr in RCA when balloon dilation couldnot be done

that is less able to stretch away from the advancing burr than is healthy arterial wall (differential cutting). High rotational speeds facilitate longitudinal burr movement across calcific lesions by orthogonal displacement of friction. A guidewire helps to keep the burr's abrasive tip coaxial with the vessel lumen, although wire bias in highly tortuous

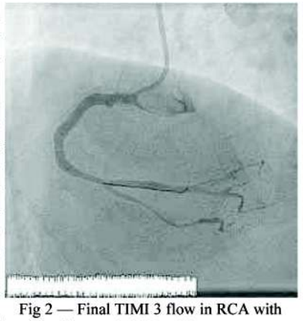

Fig 2 — Final TIMI 3 flow in RCA with well expanded 4.0 x 32 mm stent

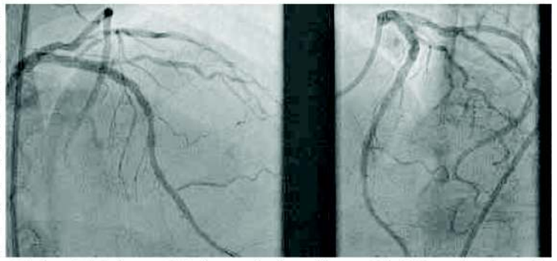

Fig 3 — Critical stenosis in the proximal to mid part of the left anterior descending artery with severe calcification and dicrete 90% stenosis in the distal part. Rotablation of the LAD with 1.5 mm burr

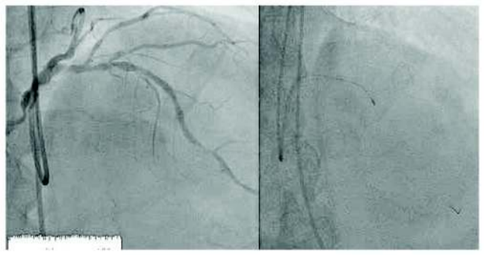

Fig 4 — Final TIMI 3 flow after 4.0 x 37 mm stent proximally and 3.0 x 16 mm stent distally

or angulated segments may predispose to dissection or perforation. Unlike balloon angioplasty, which tends to produce intimal splits and medial dissections in calcified lesions, rotablation yields a relatively smooth luminal surface with cylindrical geometry and minimal tissue injury[11,12].

In conclusion, PCI with rotablation is a safe and effective treatment strategy for calcified coronary artery disease particularly for the lesions which are non dilatable with conventional balloons. PCI with rotational atherectomy perhaps superior to CABG in calcified coronary artery disease.

References

1 Serruys PW — The SYNTAX Score: a new angiographic tool to grade the complexity of coronary artery disease. Presented at the Transcatheter Cardiovascular Therapeutics annual meeting; October 12-17, 2008; Washington, DC.
2 Vasim F — Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet* 2013; **381:** 639-50.
3 Niccoli G — Directional atherectomy before stenting versus stenting alone in percutaneous coronary interventions: a meta-analysis. *Int J Cardiol* 2006; **112:** 178-83.
4 Clavijo LC — Sirolimus-eluting stents and calcified coronary lesions: clinical outcomes of patients treated with and without rotational atherectomy. *Catheter Cardiovasc Interv* 2006; **68:** 873-8.
5 Khattab AA —. Drug-eluting stents versus bare metal stents following rotational atherectomy for heavily calcified coronary lesions: late angiographic and clinical follow-up results. *J Interv Cardiol* 2007; **20:** 100-6.
6 Bramucci E, et al. Adjunctive stent implantation following directional coronary atherectomy in patients with coronary artery disease. *J Am Coll Cardiol* 1998; **32:** 1855-60.
7 Hinohara T — Percutaneous coronary intervention: current perspective. *Keio J Med* 2001; **50:**152-60.
8 Whitlow PL — Results of the study to determine rotablator and transluminal angioplasty strategy (STRATAS). *Am J Cardiol* 2001; **87:** 699-705.
9 Cavusoglu E — Current status of rotational atherectomy. *Catheter Cardiovasc Interv* 2004; **62:** 485-98.
10 Brambilla N — Directional coronary atherectomy plus stent implantation vs left internal mammary artery bypass grafting for isolated proximal stenosis of the left anterior descending coronary artery. *Catheter Cardiovasc Interv* 2005; **64:** 45-52.
11 Mintz GS, Potkin BN, Keren G — Intravascular ultrasound evaluation of the effect of rotational atherectomy in obstructive atherosclerotic coronary artery disease Circulation 1992; **86:** 1383-93.
12 Farb A, Roberts DK, Pichard AD, Kent KM, Virmani R — Coronary artery morphologic features after coronary rotational atherectomy: insights into mechanisms of lumen enlargement and embolization. *Am Heart J* 1995; **129:** 1058-67.

(Continued from page 34)

References

1 Penaloza A, Kline J, Verschuren F — European and American suspected and confirmed pulmonary embolism populations: comparison and analysis. *J Thromb Haemost* 2012; **10:** 375–81.
2 Patel SR, Parker JA, Grodstein F, Goldhaber SZ — Similarity in Presentation and Response to Thrombolysis Among Women and Men with Pulmonary Embolism. *J Thromb Thrombolysis* 1998; **5:** 95-100.
3 Geibel A, Olschewski M, Zehender M — Possible gender-relateddifferences in the risk-to-benefitratio of thrombolysis for acutesubmassivepulmonaryembolism. *Am J Cardiol* 2007; **99:** 103-7.
4 Stein PD, Hull RD, Patel KC — Venous thromboembolic disease: comparison of the diagnostic process in men and women. *Arch Intern Med* 2003; **163:** 1689-94.
5 Kyrle PA, Minar E, Bialonczyk C, Hirschl M, Weltermann A, Eichinger S — The risk of recurrent venous thromboembolism in men and women. *N Engl J Med* 2004; **350:** 2558-63.
6 McHugh KB, Visani L, DeRosa M, Covezzoli A, Rossi E, Goldhaber SZ — Gender comparisons in pulmonary embolism (results from the International Cooperative Pulmonary Embolism Registry [ICOPER]). *Am J Cardiol* 2002; **89:** 616-9.
7 Konstantinides SV, Meyer G, Lang I — Single-bolus tenecteplase plus heparin compared with heparin alone for normotensive patients with acute pulmonary embolism who have evidence of right ventricular dysfunction and myocardial injury: Rationale and design of the Pulmonary Embolism Thrombolysis (PEITHO) trial. *Am Heart J* 2012; **163:** 33-8.e1.
8 Bandyopadhyay T, Martin I, Lahiri B — Combined thrombolysis and inferior vena caval interruption as a therapeutic approach to massive and submassivepulmonary embolism. C*onn Med* 2006; **70:** 367-70.
9 Zamanian RT, Gould MK — Effectiveness and cost effectiveness of thrombolysis in patients with acutepulmonary embolism. *Curr Opin Pulm Med* 2008; **14:** 422-6.
10 Lankeit M, Konstantinides S — Thrombolytic therapy for submassive pulmonary embolism. *Best Pract Res Clin Haematol* 2012; **25:** 379-89.
11 Kearon C, Akl EA, Comerota AJ — Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141:** e419S-94S.
12 Jaff MR, McMurtry MS, Archer SL — Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation* 2011; **123:** 1788-830.

(Continued from page 41)

6 Naofumi M, Kuniaki H, Ichiro S, Yoji O, Tsuneo M — Takayasu Arteritis: Protean Radiologic Manifestations and diagnosis. RadioGraphics. 1997; **17:** 579-94.
7 Hayashi K, Fukushima T, Matsunaga N — Ct Takayasu arteritis: decrease in aortic wall thickening following steroid therapy, documented by CT. *BrJ Radiol* 1986; **59:** 281-3.
8 Schmidt WA, Nerenheim A, Seipelt E, Poehls C, Gromnica-Ihle E — Diagnosis of early Takayasu arteritis with sonography, *Rheumatology* 2002; **41:** 496-502.
9 de Souza AWS, de Carvalho JF — Diagnostic and classification criteria of Takayasu arteritis. *Journal of Autoimmunity* 2014; 48-49, 79e83
10 Rav-Acha M, Plot L, Peled N, Amital H — Coronary involvement in Takayasu's arteritis. *Autoimmun Rev* 2007; **6:** 566e71.
11 Nastri MV, Baptista LP, Baroni RH, Blasbalg R — Gadolinium-enhanced Three-dimensional MR Angiography of Takayasu Arteritis. *Radiographics* 2004; **24:** 773-86.
12 Arnaud L, Haroche J, Malek Z, Archambaud F, Gambotti L— Is 18F-fluorodeoxyglucose positron emission tomography scanning a reliable way to assess disease activity in takayasu arteritis? *Arthritis Rheum* 2009; **60:** 1193-200. doi: 10.1002/art.24416.

(Continued from page 46)

Vaisseaux 1996; **89:** 1599-1605.
8 Lesh MD, van Hare GF, Schamp DJ — Curative percutaneous catheter ablation using radiofrequency energy for accessory pathways in all locations: results in 100 consecutive patients. *Journal of the American College of Cardiology* 1992; **6:** 1303-9.
9 Ward DE, Camm AJ — Clinical Electrophysiology of the Heart, E. Arnold, London, UK, 1987.
10 Deckers JW, M Hare, Baughman KL — "Complications of transvenous right ventricular endomyocardial biopsy in adult patients with cardiomyopathy: a seven-year survey of 546 consecutive diagnostic procedures in a tertiary referral center," Journal of the American College of Cardiology 1992; **19:** 43-7.
11 Seggewiss H, Schmidt HK, Mellwig KP — Acute pericardial tamponade after percutaneous transluminal coronary angioplasty (PTCA). A rare life threatening complication. *Zeitschrift f˙ur Kardiologie* 1993; **82:** 721-26.

Activities Report

IMA Hubli Branch Organised CME, Doctors' Day, 72nd Independence Day

IMA Thrissur Branch Organised Plastic Surgery Day, Health Quiz, CME, World Hepatitis Day, D-Day & Basic Life Support programme

IMA North Paravur Branch Organised Health Camp, Flood Relief Camp

Activities Report

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