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Environmental Stress and Cardiovascular Disease

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Environmental stressors like air pollution and extreme temperatures have multiple deleterious effects on cardiovascular health, which have all but been ignored. Lately, in concert with the cry to attend to the current and upcoming calamities caused by climate change, are a chorus of cardiologists ensuring that the impacts on the heart are also considered.

"While we face the existential crisis of climate change, most people don't realize that of the many deleterious effects of air pollution, cardiovascular disease is #1. It's not diseases of the lung or cancer, but it's in fact ischemic heart disease and stroke that top the list," says Jamal S. Rana, MD, PhD, FACC, chief of cardiology at Kaiser Permanente's Oakland Medical Center and governor of ACC's Northern California Chapter.

Every Breath You Take

The Global Burden of Disease (GBD) consortium found that pollution accounted for 9 million deaths worldwide in 2019. Of these, over 5 million were due to cardiovascular disease.

Air pollution is split into two categories – ambient particulate matter (<2.5 μm [PM2.5]) and household air pollution. Household air pollution is primarily a result of indoor use of dirty solid fuels (e.g., coal, wood, agricultural waste, etc.). It is a substantial (albeit declining) contributor to cardiovascular mortality in low-income countries.

Ambient air pollution arises principally from fossil fuel combustion and is a problem worldwide. Fine particulate matter refers to particles with an aerodynamic-mass median diameter <2.5 μm. To give an idea of the size of these particles, the average human hair is 70 μm in diameter.

The bad news is that, beyond air pollution, the burning of fossil fuels is changing our climate by increasing levels of heat-trapping pollution such as carbon dioxide in the Earth's atmosphere. Those rising temperatures are fuelling more extreme weather and contributing to dangerous heat waves, dramatic spikes in air pollution, a surge in wildfires, and other issues that are expected to trigger marked increases in harm to public health.

"Due to the warmer climate, we're pretty well locked into a future of more wildfires, more frequent wildfires, a longer wildfire season, and more severe wildfires that are very difficult, if not impossible, to suppress," The wildfires are serving to increase awareness of air pollution.

Don't Go Breaking My Heart

There is a wealth of data showing the effects of air pollution on the whole spectrum of cardiovascular disease, from myocardial infarction (MI) to stroke, to cardiac arrest, heart failure exacerbation and arrhythmias. Elevated levels of particulate matter in the air increase the relative risk of acute cardiovascular events by 1% to 3% within a few days. Longer-term exposure increases this risk by about 10%, says Sanjay Rajagopalan, MD, and colleagues in a JACC state-of-the-art review. Air pollution has also been associated with an increased risk of atrial fibrillation and ventricular arrhythmias.[2]

Long-term exposure to ambient PM2.5 has also been linked to subclinical cardiovascular disease such as left ventricular hypertrophy, increased carotid intima media thickness, and calcification of both the coronary artery and abdominal aorta.

In 2019, about 99% of the world population was living in places where the World Health Organization air quality guidelines of <10 mg/m^3 for annual levels and <20 mg/m^3 for daily levels were not met. Prolonged exposure to PM2.5 at 50 μg/m^3 doubles the risk of developing cardiovascular diseaes.

The pathophysiologic mechanisms and biologic pathways through which PM2.5 triggers cardiovascular events are numerous. A scientific statement from the American Heart Association suggests that acute and chronic inhalation of particulate matter initiates extrapulmonary effects on the cardiovascular system via three broad "intermediary" pathways: 1) the release of proinflammatory mediators or vasculoactive molecules; 2) perturbation of the autonomic nervous system balance or heart rhythm by particle interactions

MORTALITY RISK FACTORS – 2019 RANK
1. High systolic blood pressure
2. Tobacco
3. Dietary risks
4. Air pollution
4. High fasting plasma glucose
6. High body-mass index
7. High LDL cholesterol
8. Kidney dysfunction
9. Child and maternal malnutrition
10. Alcohol use
11. Non-optimal temperature
12. Unsafe water, sanitation and handwashing

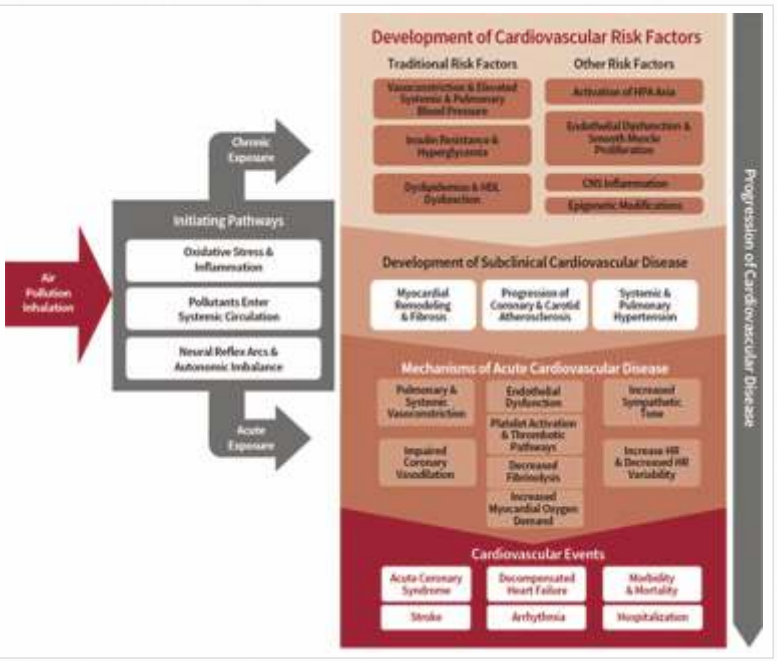
Mortality Risk Factors, Both sexes, all ages, 2019. Institute for Health Metrics and Evaluation. (Adapted from Institute for Health Metrics and Evaluation, 2020). Brauer et al. *J Am Coll Cardiol* 2021;77:1684-8.

with lung receptors; and, 3) potentially, the translocation of particulate matter or particle constituents directly into the systemic circulation.

According to a recent report from the World Heart Federation Air Pollution Expert Group, globally, air pollution ranked the fourth highest among risk factors for mortality, beating out high LDL-C, high body mass index, physical inactivity and alcohol use.

The Heat is On

Scorching heat, deadly floods, wildfires, drought. Around the world, climate change continues to make the unprecedented precedented, and to deadly effect.



Deaths attributable to heat stroke are actually a minority of the overall deaths attributed to extreme heat. Similar to air pollution, it's the deaths from cardiovascular and cerebrovascular disease that are likely the more important contributor to overall heat-related deaths.

Age is an important factor, with the elderly shouldering the lion's share of the heat-related increase in death. Some of the reasons for this are logistic-elderly people are more likely to have physical and socioeconomic limitations that limit their ability to manage extreme heat events.

But there are a number of physiological changes associated with aging that also predispose older folks to heat-related circulatory collapse. Older adults produce less sweat so they have less evaporative cooling efficiency, a problem exacerbated by the fact that elderly people are less able to redirect blood flow away from the deep splanchnic vasculature to the skin to facilitate cooling. Also, the aging heart has weaker contractile force in response to heat, limiting cardiac output in response to drops in blood pressure and left ventricular preload (both of which are a response to dehydration).

These physiologic limitations are particularly intensified in older adults with cardiovascular disease, many of whom are also taking medications that further increase vulnerability to heat. For example, diuretics increase dehydration risk and beta-blockers reduce the heart's ability to augment rate and stroke volume in response to increased circulatory demand.

Shelter From the Storm

Obviously, climate change requires a societal response. Yet, there are important patient-level and community-level activities that can mitigate risk.

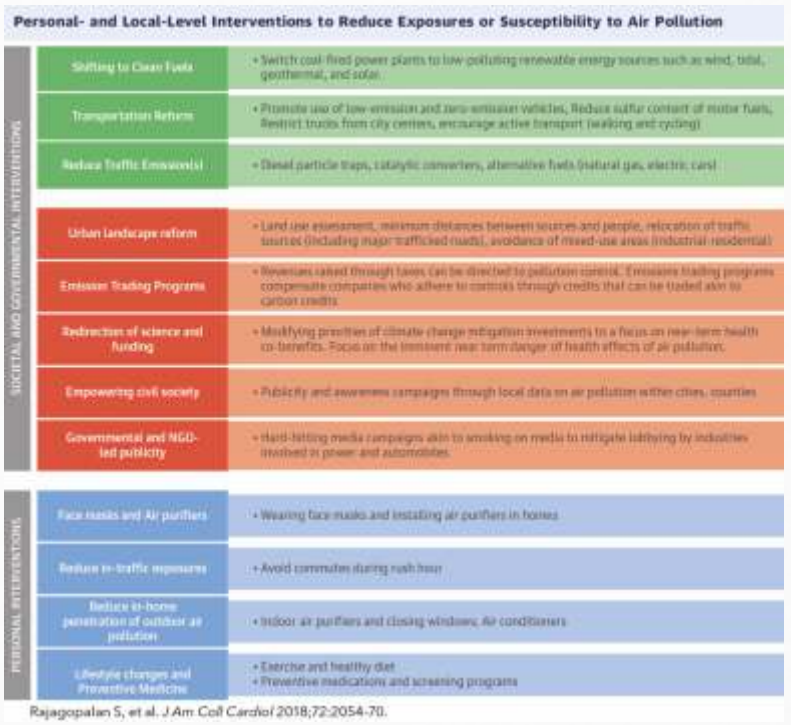
Importantly, health care providers should screen older patients regularly to assess their level of vulnerability to weather-related events and provide personal risk mitigation strategies. One simple solution on bad air days is face masks. It's hard to say there are any silver linings to COVID, but certainly people are more accepting and attuned to wearing N95 masks on bad air days than they were before.

Environmental stressors should be included in the list of risks we discuss with patients. Along with talking with a patient about a better diet, more exercise and taking their medications, clinicians should routinely discuss wearing a mask or taking other measures when exposure could be high. "This would be a big step forward" along with acknowledging that a patient lives in a high pollution area and how that might impact their health status.

Clinicians also need to provide vulnerable patients with personal management plans which is a combination of ensuring patients have access to their clinical care and their medications in the event they are displaced by an event. Add to that access to personal protective equipment and HEPA filtration devices. which might entail providing these items to low-income populations. As well as making sure they have access to clean air shelters during a wildfire, cooling stations during extreme heat events, etc.

Most personal mitigation strategies have not been formally tested and shown to reduce clinical events, but some have been shown to at least improve some biomarkers of cardiometabolic health. Portable air filters can lower indoor PM2.5 levels by >50% and are proven to improve a growing list of surrogate endpoints, including blood pressure, insulin sensitivity, inflammatory markers, stress hormones and metabolomic profiles.

Clinicians have a role to play in raising awareness and advocating for change, in general, but for air pollution specifically. Understanding that it's a risk factor for cardiovascular disease and understanding that an improvement in air quality will equitably and efficiently benefit everyone is really important.



Rajagopalan S, et al. *J Am Coll Cardiol* 2018;72:2054-70.

Bionic pancreas improves type 1 diabetes management compared to standard insulin delivery methods

Next-generation technology maintains blood glucose levels by automatically delivering insulin.

A device known as a bionic pancreas, which uses next-generation technology to automatically deliver insulin, was more effective at maintaining blood glucose (sugar) levels within normal range than standard-of-care management among people with type 1 diabetes, a new multicenter clinical trial has found. The trial was primarily funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), part of the National Institutes of Health, and published in the New England Journal of Medicine(link is external).

Automated insulin delivery systems, also called artificial pancreas or closed-loop control systems, track a person's blood glucose levels using a continuous glucose monitor and automatically deliver the hormone insulin when needed using an insulin pump. These systems replace reliance on testing glucose level by fingerstick, continuous glucose monitor with separate insulin delivery through multiple daily injections, or a pump without automation.

Compared to other available artificial pancreas technologies, the bionic pancreas requires less user input and provides more automation because the device's algorithms continually adjust insulin doses automatically based on users' needs. Users initialize the bionic pancreas by entering their body weight into the device's dosing software at the time of first use.

Users of the bionic pancreas also do not have to count carbohydrates, nor initiate doses of insulin to correct for high blood glucose. In addition, health care providers do not need to make periodic adjustments to the settings of the device.

"Keeping tight control over blood glucose is important in managing diabetes and is the best way to prevent complications like eye, nerve, kidney, and cardiovascular disease down the road," said Dr. Guillermo Arreaza-Rubín, director of NIDDK's diabetes technology program. "The bionic pancreas technology introduces a new level of ease to the day-to-day management of type 1 diabetes, which may contribute to improved quality of life."

The 13-week trial, conducted at 16 clinical sites across the United States, enrolled 326 participants ages 6 to 79 years who had type 1 diabetes and had been using insulin for at least one year. Participants were randomly assigned to either a treatment group using the bionic pancreas device or a standard-of-care control group using their personal pre-study insulin delivery method. All participants in the control group were provided with a continuous glucose monitor, and nearly one-third of the control group were using commercially available artificial pancreas technology during the study.

In participants using the bionic pancreas, glycated hemoglobin, a measure of a person's long-term blood glucose control, improved from 7.9% to 7.3%, yet remained unchanged among the standard-of-care control group. The bionic pancreas group participants spent 11% more time, approximately 2.5 hours per day, within the targeted blood glucose range compared to the control group. These results were similar in youth and adult participants, and improvements in blood glucose control were greatest among participants who had higher blood glucose levels at the beginning of the study.

"Our observation that this system can safely improve glucose control to the degree we found, and do so despite requiring much less input from users and their health care providers, has important implications for children and adults living with diabetes," said Dr. Steven Russell, study chair, associate professor of medicine at Harvard Medical School, and staff physician at the Massachusetts General Hospital in Boston.

Hyperglycemia, or high blood glucose, caused by problems with insulin pump equipment, was the most frequently reported adverse event in the bionic pancreas group. The number of mild hypoglycemia events, or low blood glucose, was low and was not different between the groups. The frequency of severe hypoglycemia was not statistically different between the standard of care and bionic pancreas groups.

Four companion papers were also published in Diabetes Technology and Therapeutics, two of which provided more detailed results among the adult and youth participants. The third paper reported results from an extension study in which the participants from the standard-of-care control group switched to using the bionic pancreas for 13 weeks and experienced improvements in glucose control similar to the bionic pancreas group in the randomized trial. In the fourth paper, results showed that using the bionic pancreas with a faster-acting insulin in 114 adult participants improved glucose control as effectively as using the device with standard insulin.

"NIDDK's decades-long investment in developing advanced technologies for diabetes management has reached another promising milestone and continues to provide significant return," said NIDDK Director Dr. Griffin P. Rodgers. "While we continue to search for a cure for type 1 diabetes, devices like the bionic pancreas can allow people to worry less about their blood-glucose levels and focus more on living their fullest, healthiest lives."

Dr. Edward Damiano, project principal investigator, professor of biomedical engineering at Boston University, and founder and executive chair of Beta Bionics, Inc., concurs. "The completion of this study represents a major milestone for the bionic pancreas initiative, which simply would not have been possible had it not been for the support provided by the NIDDK over the years."

The study is one of several pivotal trials funded by NIDDK to advance artificial pancreas technology and look at factors including safety, efficacy, user-friendliness, physical and emotional health of participants, and cost. To date, these trials have provided the important safety and efficacy data needed for regulatory review and licensure to make the technology commercially available. The Jaeb Center for Health Research in Tampa, Florida, served as coordinating center.

Ref: https://www.nih.gov/news-events/news-releases/bionic-pancreas-improves-type-1-diabetes-management-compared-standard-insulin-delivery-methods

Case Study - 1

Robotics in Interventional Cardiology: A Case-based Appraoch

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MD-Medicine, DM-Cardiology, Nashik

and **Dr. Ganesh Jagdale**

Case Presentation

A 65-year-old female patient, known case of hypertension and type 2 diabetic mellitus with past history of transient ischemic attack in the year 2012, was referred to our hospital with evolving inferior wall myocardial infarction (4 days old), which was duly thrombolyzed with tenecteplase. Patient had persistent class III dyspnea and class III angina with ECG showing persistent ST elevations. She also had history of fever with altered sensorium with decreased urine output.

On admission, her heart rate was 110/min, blood pressure was 90/50 mmHg maintained with moderate dose of noradrenaline infusion. Her respiratory rate was 22/min with SPO2 of 84% on room air.

Initial diagnosis of evolving inferior wall myocardial infarction with cardiogenic shock with urosepsis with acute kidney injury was made. She was started on necessary management including dual antiplatelets, anticoagulation, statins,

and higher antibiotics along with diuretics, oxygen supplementation and continuation of noradrenaline infusion.

In view of hemodynamic instability after necessary counseling of the relatives and consent, she was taken for emergency rescue coronary angioplasty which showed a very long segment lesion with subtotal occlusion in the mid part of RCA with minimal thrombus. Using ROBOTIC Guidance, successful percutaneous angioplasty was done covering the long lesion segment with a SINGLE 60 mm stent. Patient did well and was discharged from the hospital after 4 days. Nearly 1-year follow-up with the patient has been uneventful.

Clinical Discussion:

Laboratory Investigation:

Hemogram showed hemoglobin of 10.2 gm/dl, total WBC count of 15,300/cmm with neutrophilic predominance, platelet count of 2.62 lakh/dl, serum creatinine 2.2 mg/dl, serum urea of 67.9 mg/dl. Post stabilization, creatinine came down to 0.9 mg/dl and serum urea came down to 34.9 mg/dl. Urine showed plenty of pus cells. Procalcitonin was 0.62 ng/ml. HbA1C was 10.9%.

Electrocardiogram showed QS in leads III and aVF along with mild ST elevations in leads II, III, aVF (Fig. 1). Echocardiography showed basal and mid-inferior and basal and mid-posterior wall akinesia with preserved wall thickness with LVEF of 40%, with trivial mitral regurgitation and trivial tricuspid regurgitation with grade I diastolic dysfunction, with mild pulmonary hypertension with estimated pulmonary artery systolic pressure of 45 mmHg.

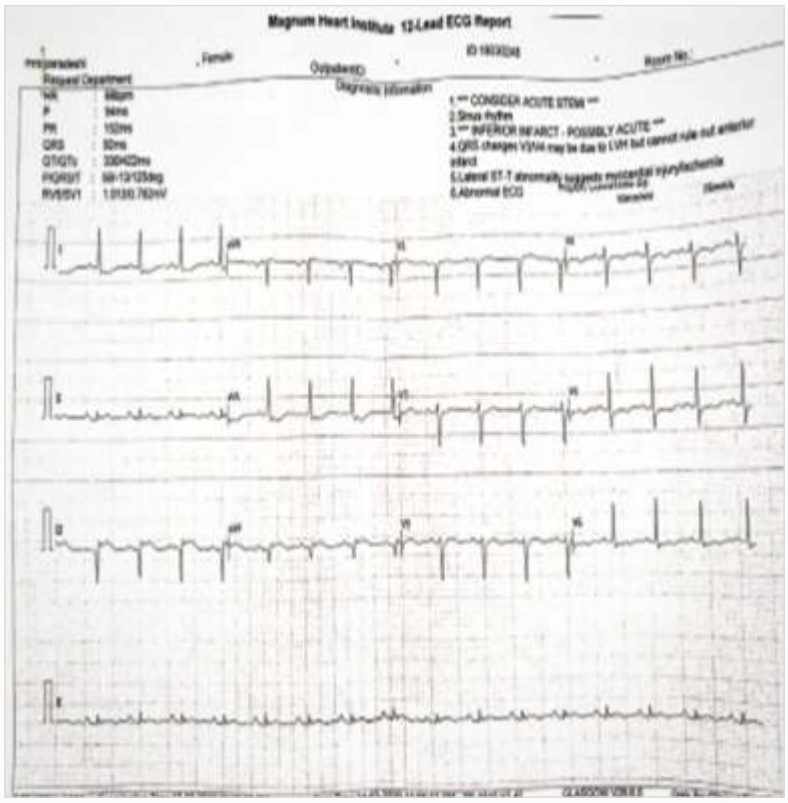


Fig. 1: Electrocardiogram showing QS in leads III and aVF along with persistent ST elevations

Ultrasound of abdomen revealed mild generalized hepatomegaly, both kidneys were bulky with smooth margins with increased echogenicity more prominent on left side. Rest of the investigations were within normal limits.

Management Issues:

As seen in the Video 1, patient's coronary angiogram revealed very long segment, partially critical thrombotic lesion in the RCA starting from the proximal part extending till distal portion. Fig. 2 shows left system which did not have any significant lesion. Long difuse lesion needed to be assessed accurately in terms of the length. As we wanted to avoid stent overlap by putting 2 stents, feasibility of single long stent placement needed to be assessed. Also, as patient was in cardiogenic shock and had acute kidney injury, putting single stent instead of 2 stents could potentially minimize the contrast use. In-built measuring tool in the robotic arm helped in measuring the lesion length accurately.

Putting a long stent in critically diseased vessel is always a challenge because of difficulties faced in tracking the stent down the diseased vessel. This requires good guide support which is provided by the robotic arm which holds the guide firmly in place while we can push the stent in.

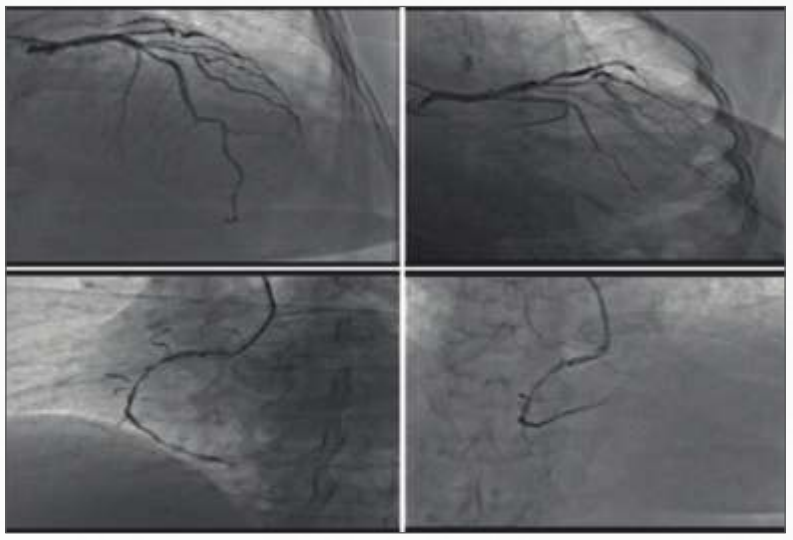


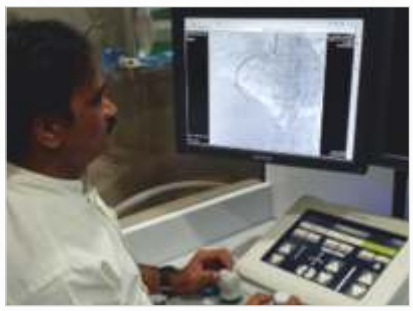
Fig. 2: Coronary angiogram showing long segment dif use disease in RCA and mild disease in left system

As seen in Fig. 3, the high-resolution monitor which is in close proximity to the eyes of the primary operator, gives excellent visualization of the vessel anatomy, so that the possibility of the geographical miss is minimized. Precise 1 mm movement of the stent which is possible with the robotic arm helps in predictable and accurate movements of the stent, so that repeated use of contrast injections is avoided. The 'rotate on retraction' feature given in the robotic arm helps easier maneuvering of the wire through tortuous arteries. Hence, use of the robotic assisted PTCA to RCA was planned.

Procedure:

RCA cumulated with 6F JR 3.5 guide catheter with the help of robotic arm. Powerturn wire was used to cross the lesion and it was parked in distal RCA. Traveler 2.5 x 15 mm balloon was used to cross the lesion and gradual inflations were given from distal to proximal part and the lesion bed was well prepared. Lesion length which was calculated by QCA & Robotic measurement was around 57 mm, so Biomime Morph 3.0- 2.5 x 60 mm DES stent positioned and deployed across the lesion. As seen in Video 2 the 60 mm stent could be easily tracked on regular coronary wire without much difficulty. Post dilatation was done using Sprinter NC 3.0 x 15 mm NC balloon at high pressure. As seen in Video 3, after Post dilatation we had a very good result with TIMI III flow achieved.

Fig. 3 shows the still picture of the end result.



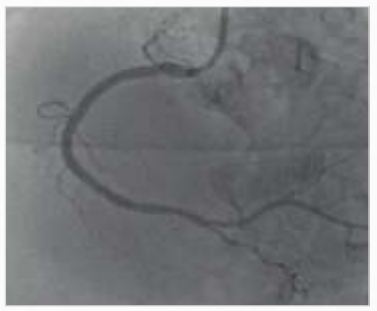


Fig. 4: Image from robotic console showing high quality close view of coronary anatomy

Fig. 5: Good post-stent result in RCA

Why this Case was Chosen

We have Corindus CorPath GRX system with us, which is basically a system for robotic assisted cardiac intervention developed by Corindus healthcare. The CorPath System is the first FDA-cleared robotic platform designed for interventional cardiologists. It has been installed since almost 1 year 3 months and we have completed more than 325 cases on this machine. The CorPath Vascular Robotic Program is the first and only robotic program for interventional cardiologists. There are only four installations of this machine in India and very few in the rest of the world. Though it has many proven benefits, since it's a newer technology, its use for doing complex coronary cases is limited. Ours is the first case of putting a 60 mm long stent in a coronary artery using this technology.

As most of the initial experience of this modality is from the Western world where stents more than 48 mm in length are generally not used, so the usefulness of this system in tracking the longer stents is not well documented. As the robotic arm holds the catheter and the coronary guide wire firmly in place, tracking the longer stents, which is difficult at times because of catheter backing, is negated and pushing the stent is relatively easy.

Expert Opinion: SGLT2 Inhibitors Beyond Diabetes

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Introduction:
Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are novel antidiabetic agents with overwhelming cardiorenal protection. Recent trials focusing on the nephroprotective role of SGLT2i have underscored its success as a phenomenal agent in halting the progression of kidney disease in patients with and without Type 2 diabetes mellitus. Multitudes of pleiotropic effects on tubules have raised hopes for reasonable nephroprotection beyond the purview of the hyperglycemic milieu.

Area covered:
This review summarizes various animal and human data as evidence for the utility of SGLT2i in non-diabetic chronic kidney disease (CKD). Web-based medical database entries were searched. On the premise of existing evidence, we have discussed mechanisms likely contributing to nephroprotection by SGLT2i in patients with non-diabetic CKD.

1. Introduction
Recent interest in sodium-glucose cotransporter-2 inhibitors (SGLT2i) have been drawn by the findings of large multicenter randomized trials primarily designed to satisfy FDA regulations. Results of these trials have crowned SGLT2i as cardio-renal risk-reducing agents with blood glucose-lowering as their beneficial side effect. Findings like the reduced incidence of cardiovascular death and heart failure-related hospitalization, reduction in albuminuria, and slowing of annual estimated glomerular filtration rate (eGFR) decline among albuminuric diabetic chronic kidney disease (CKD) patients outline their organ protective effects. Considering the understanding that the underlying nephro- and cardioprotective mechanisms of SGLT2i are independent of their blood glucose-lowering effect, similar benefits are expected in non-diabetic CKD patients treated with SGLT2i.

In this review, we discuss various preclinical and clinical studies that address possible mechanisms of nephroprotection offered by SGLT2i in states of non-diabetic CKD.

2. SGLT2i and their nephroprotective action
Raised intraglomerular pressure with resultant hyperfiltration leads to CKD progression, as highlighted by Brenner's seminal work in the early 90s [9]. In health, a protective feedback system (TGF), gets activated in response to increased salt delivery to the MD cells and reduces GH via adenosineinduced afferent vasoconstriction. GH is accompanied by enhanced proximal tubular reabsorption of solutes through increased expression of various cotransporters.

Persistent GH and accentuated proximal tubular reabsorption in diseased states limit solute delivery to MD, which eventually downregulate TGF, and in turn results in rebound GH. SGLT2i block both the cotransporters and increase the delivery of solutes to the MD cells and keep the TGF activated. SGLT2i, akin to low protein intake and renin-angiotensinaldosterone system (RAAS) blockers, tends to mitigate intraglomerular pressure and protect single nephron GFR (SNGFR). However, SGLT2i, unlike RAAS blockers, primarily works by inhibiting excessive proximal tubular resorption, rather than just mechanically reducing GH directly. Adenosine mediates SGLT2i-induced reduction of GH via pre-glomerular constriction in Type 1 diabetes mellitus (DM) and postglomerular dilatation in Type 2 DM. SGLT2 cotransporter inhibition in non-diabetic and Akita Sglt1-/- mice also mitigates MD-derived nitric oxide-dependent increase in GFR, possibly through changes in volume status

Significant albuminuria reduction has been noted among diabetic subjects both in preclinical as well as clinical studies. The Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy (CREDENCE) trial has been instrumental in making SGLT2i a quantum leap in retarding CKD progression. Exploratory analysis of the study has linked long-term kidney outcomes to early albuminuria reduction. Alteration in glomerular hemodynamics has been attributed to albuminuria reduction caused by SGLT2i. While albuminuria reduction follows a decline in GFR during the initial weeks of therapy, sustained albuminuria reduction up to 2 years has been documented to be associated with improvement in long-term GFR. In a post hoc analysis of stage 3 CKD patients treated with Dapagliflozin, albuminuria reduction was maintained even after adjustment for change in GFR, blood pressure, HbA1c, and uric acid reduction were made. These findings suggest that perhaps renal hemodynamics alterations only partly explain sustained albuminuria reduction with SGLT2i. In that case, what underlying mechanisms ensure the continued benefits of these agents is yet to be known.

3. Are SGLT2i the same as RAAS blockers?
Most drugs in the armamentarium of therapeutics for glomerular disease address albuminuria as a target. Over several decades, RAAS blockers have been crucial agents causing both albuminuria reduction and GFR stabilization. Of late, clinical trials had shown augmented albuminuria reduction when SGLT2i was added in patients already on with a maximal dose of RAAS blockers. The addition of canagliflozin to maximum tolerable RAAS blockade reduced urine albumin creatinine ratio (ACR) by a further 31%. Also, it lowered the slope of eGFR decline by additional 1.52 mL/min/ 1.73 m2 per year, without any excess risk of acute kidney injury (AKI). Safety analysis confirms the complementary utility of these agents without excess risk of AKI in advanced CKD participants of the CREDENCE trial.

Table 1. Clinical studies assessing SGLT2i in the euglycemic milieu.

Study	Design	Study participant	Investigational drug	Kidney related outcome	Other outcomes
DAPA CKD Heerspink et al. [6]	Randomized controlled trial	CKD with or without T2D (67.5% had T2D)	Dapagliflozin and placebo (N = 4304)	Dapagliflozin reduced primary outcome[a] Hazard ratio- 0.61 (95% CI: 0.51–0.72; p < 0.001)	Similar benefit afforded by patients irrespective of diabetes
Cherney et al. [23]	Double-blind, randomized placebo-controlled trial (cross over design)	CKD without diabetes	Dapagliflozin and placebo (N = 53) for 6 weeks	A reversible decline in lohexol-mGFR seen with dapagliflozin, No change in proteinuria and blood pressure	Bodyweight reduction noted
Rajasekeran et al. [34]	Open label pilot study	Biopsy proven FSGS (primary & secondary)	Dapagliflozin (10 mg/day) N = 10 for 8 weeks	No change in filtration fraction, Renal plasma flow, non-significant GFR decline	Increased hematocrit
Zanchi et al. [82]	Randomized placebo-controlled trial	healthy volunteers	Empagliflozin (N = 30), placebo (N = 15)	Sustained glucosuria and transient natriuresis, blood pressure reduction	No acute or sustained changes were found in renal cortical or medullary tissue oxygenation on BOLD-MRI.

SGLT2i: sodium-glucose co transporter-2 inhibitor; FSGS: focal segmental glomerular sclerosis; mGFR: measured glomerular filtration rate; T2D: Type 2 diabetes; BOLD-MRI: blood-oxygenation-level-dependent magnetic resonance imaging; [a]primary outcome: sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal causes.

In contrast, a similar attempt to augment GH reduction by potentiating RAAS inhibition using two types of RAAS blockers resulted in an increased risk of hyperkalemia and AKI. It is plausible that the compound GH reduction through different mechanisms (afferent vasoconstriction versus efferent vasorelaxation) might underlie the add-on benefits of the combination therapy of SGLT2i and RAAS blockers.

However, unlike RAAS blockers, albuminuria reduction with SGLT2i is quite variable. Petrykiv et al. have detected substantial interindividual variability in 24- h urine albumin excretion reduction with SGLT2i. In another crossover trial design, the same authors have confirmed inter-individual variability in albuminuria reduction while on SGLT2i. The reason for such variability in albuminuria reduction with SGLT2i in these studies is not apparent and might reflect a heterogenous study population. The author found a significant correlation between dapagliflozin response and response to RAAS Blockers, which indicates the addition of Dapagliflozin overcomes resistance to RAAS blockers by restoring TGF.

4. The inception of SGLT2i's role in non-diabetics
The first proof of nephroprotective efficacy of SGLT2i in nondiabetic CKD came from two large trials on patients with heart failure, which included kidney disease patients with baseline eGFR as low as 20 ml/min and 30 ml/min, respectively. Results upheld cardiac as well as nephroprotection beyond doubt, alike in both groups. Apart from establishing proof of concept for nephroprotection among non-diabetics, these trials have also highlighted drug tolerability in CKD patients up to an eGFR of 20 ml/min. A meta-analysis of these studies had confirmed cardiac benefits (risk reduction of worsening heart failure or CV death) irrespective of the presence of DM, with a hazard ratio (HR)

for diabetic and non-diabetic patients being [0.74 (95% CI 0.65-0.84)] and [0.75 (95% CI 0.65-0.87)], respectively. The EMPEROR-reduced trial showed a statistically significant reduction in the prespecified renal composite endpoint with HR 0.50 [95% CI, 0.32-0.77].

Conclusion:

The nephroprotective action of SGLT2i is independent of their anti-glycemic potential and eminent clinical trials have suggested nephroprotection among CKD of nondiabetic origin. Uncertainty exists regarding the predominant mechanism of nephroprotection by these agents. It is through the existing various pleiotropic tubular effects that the utility of SGLT2i in non-diabetic CKD seems to be assuring. While renal hemodynamic alteration is believed to cause albuminuria reduction by SGLT2i, it may also reflect a reduction in inflammatory milieu & oxidative stress, anti-fibrotic effect, and improvement in tubular health brought by these agents. Emerging evidence has supported the complementary utility of SGLT2i along with RAAS blockers due to added advantages. Additional 'off target' effects like blood pressure reduction, systemic sympathetic antagonism, and body weight reduction have been consistently present in patients without DM. The role of low energy sensors activation by these agents is yet to be fully elucidated. Thus, the use of SGLT2 inhibitors in patients other than DM appears promising. Nevertheless, it is crucial to know its use in other patient populations and the best timing of starting these agents during the natural history of kidney disease.

Expert opinion

SGLT2is are unique tubular diuretics with the potential to recuperate proximal tubular epithelial cells. Encouraging results in non-diabetic kidney disease have increased the dubiety of pinpointing one nephroprotective mechanism of SGLT2i. The most notable nephroprotective mechanism of SGLT2i is the dynamic control of glomerular hyperfiltration through modulation of tubulo-glomerular cross talk, i.e. TGF rejuvenation. TGF rejuvenation also underpins the effectiveness of SGLT2i in overcoming resistance to RAAS blockers in diabetic and non-diabetic CKD. Regulation of fuel economics and reallocation of energy-demanding electrolyte transporters help in offloading of proximal tubules. Restoration of redox signaling pathways (AMPK and SIRT1), induction of autophagy, amelioration of mitochondrial morphologic abnormalities, suppression of inflammatory & profibrotic processes, and preservation of renal capillary network through increased expression of VEGF-A are other important protective mechanisms of these agents. The individual contribution of these mechanisms toward nephroprotection is unknown as it is difficult to gauge their impact on clinical outcomes like albuminuria reduction and lowering of eGFR slope. Yet, the understanding of these nephroprotective mechanisms at the molecular level is likely to extend the clinical use of SGLT2i further and better characterize an appropriate timing of starting these agents in patients at risk of CKD.

Ref: https://doi.org/10.1080/17512433.2021.2028620

PRODUCT UPDATE

Dapagliflozin Proves HFpEF Benefit in DELIVER Trial

Dapagliflozin reduces the risk of cardiovascular death or worsening heart failure in heart failure patients with mildly reduced and preserved ejection fraction, according to results of DELIVER trial.

"Taken together with previous research in heart failure patients with reduced ejection fraction, data suggest that dapagliflozin is effective regardless of ejection fraction and support the use of SGLT2 inhibitors as foundational therapy in all patients with heart failure."

DELIVER was designed to determine whether dapagliflozin would decrease cardiovascular morbidity and mortality in patients with heart failure with mildly reduced or preserved ejection fraction, a group for whom limited therapies are available.

DELIVER was a randomized, double-blind, placebo-controlled trial conducted at 353 sites in 20 countries. The trial enrolled patients aged 40 years and above with symptomatic heart failure with an ejection fraction of greater than 40% who were either chronic outpatients, hospitalized or recently hospitalized, including patients who previously had an ejection fraction of 40% or below (i.e. heart failure with improved ejection fraction). Patients were randomized to dapagliflozin or placebo and followed for a median of 2.3 years. The primary endpoint was a composite of cardiovascular death or worsening heart failure.

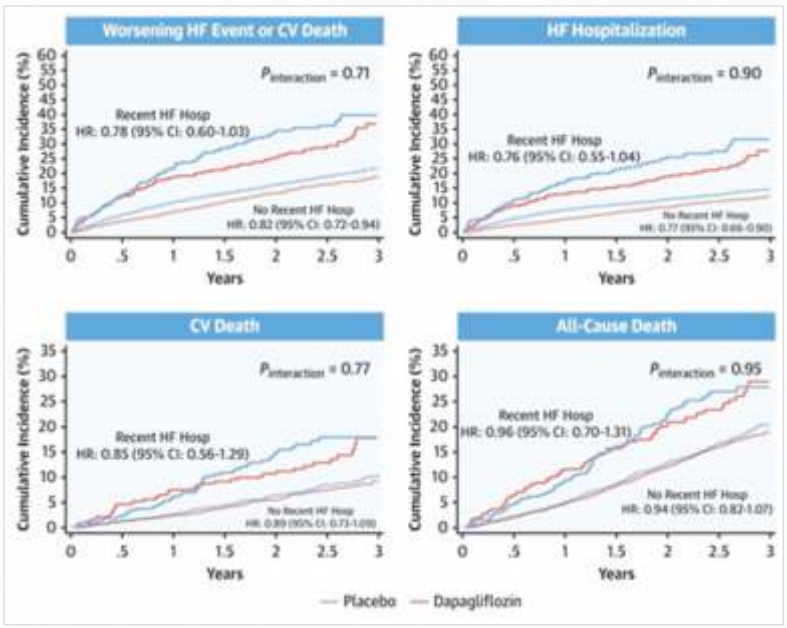
A total of 6,263 patients were randomly allocated to dapagliflozin, 10mg once daily, or placebo. The average age of participants was 72 years and 44% were women. The average left ventricular ejection fraction was 54%, and 18% of patients previously had an ejection fraction of 40% or less. At randomization, 77% of patients were taking an angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB) or angiotensin receptor neprilysin inhibitor (ARNI), 83% were taking a beta blocker and 43% were taking a mineralocorticoid receptor antagonist (MRA).

Over a median 2.3 years, the primary outcome occurred in 512 of 3,131 patients (16.4%) in the dapagliflozin group and 610 of 3,132 patients (19.5%) in the placebo group (hazard ratio [HR] 0.82; 95% confidence interval [CI] 0.73-0.92; $p<0.001$).

Outcome:

Dapagliflozin significantly reduced the primary composite endpoint by 18%, with numerically lower rates of all components of the primary endpoint. These benefits were consistent across prespecified subgroups, with similar benefits in patients with ejection fraction at, below, or above 60%, those with heart failure with improved ejection fraction, as well as in patients who were hospitalized recently, and was accompanied by improvement in symptoms.

In a previous trial (DAPA-HF; Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure), dapagliflozin reduced the risk of worsening heart failure or cardiovascular death among patients with heart failure and a left ventricular ejection fraction of 40% or less. The results of the DELIVER trial extend those of the DAPA-HF trial to patients with heart failure and a left ventricular ejection fraction of more than 40%



CASE STUDY - 2

Rota ablation in saphenous venous graft intervention.

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Introduction

Rota ablation is used tool for Coronary artery percutaneous transluminal angioplasty; herein we present a rare case of Rota ablation in Saphenous Venous Bypass Graft with Graft age more than 20 year.

Case Details

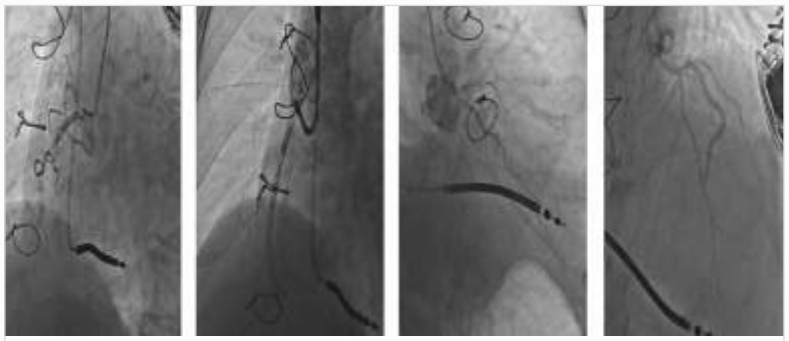
An 84 year male with Type II Diabetes Mellitus since 25 years, Hypertensive since 20 years on regular medications. He underwent Coronary Bypass Graft Surgery (CABG) 24 year back (1986) with LIMA LAD, SVG PDA OM Grafts. He also underwent AICD insertion in 2012. He was admitted in other hospital for Acute Left Ventricular Failure (LVF) with Angina. He was being managed medically, but in view of persistent LVF he was transferred to our Centre for further management. His electrocardiograph showed sinus rhythm with qs in

Lead III.Echocardiography showed Inferior, Inferiolateral wall hypokinesia, Anterolateral wall Akinesia with preserved wall thickness with moderate LV dysfunction with LV Ejection Fraction of 35%, with moderate mitral regurgitation, mild tricuspid regurgitation with moderate pulmonary hypertension and grade I diastolic dysfunction. Relevant Lab tests were done, which showed raised troponin levels, BNP level was 1230 pg/dl, Hb: 13.7 gm%, WBC count: 7500 cumm, Platelet counts: 1, 81,000/dl, Serum Creatinine: 1.3 mg/dl, HbA1C of 7.0%.

He was stabilized with Dobutamine infusion, diuretics, antiplatelet, anticoagulant, atorvastatin, anti-hypertensive medications, insulin as per blood sugars.

CARDIAC CATHETERISATION VIA Right Radial Showed:

Patent LIMA to LAD graft, SVG to RCA graft showed proximal 90% thrombotic appearing lesion with tram track calcification and occluded sequential SVG Graft from PDA to OM. Native vessel disease showed proximal total LAD occlusion, Left circumflex is non dominant vessel is diffusely diseased, Dominant RCA totally occluded from Mid segment, SVG to RCA Graft PCI with distal protection device was planned for him.



(A) NATIVE RCA (B) SVG TO PDA (C) NATIVE LEFT SYSTEM (D) LIMA TO LAD

a) Native RCA totally occluded from Mid Segment, b) SVG to RCA graft showed proximal 90 % thrombotic appearing lesion with tram track calcification and occluded jumping SVG Graft from PDA to OM, c) Native Left system proximal LAD total occlusion, Left circumflex is non dominant vessel is diffusely diseased, d) Patent LIMA to LAD

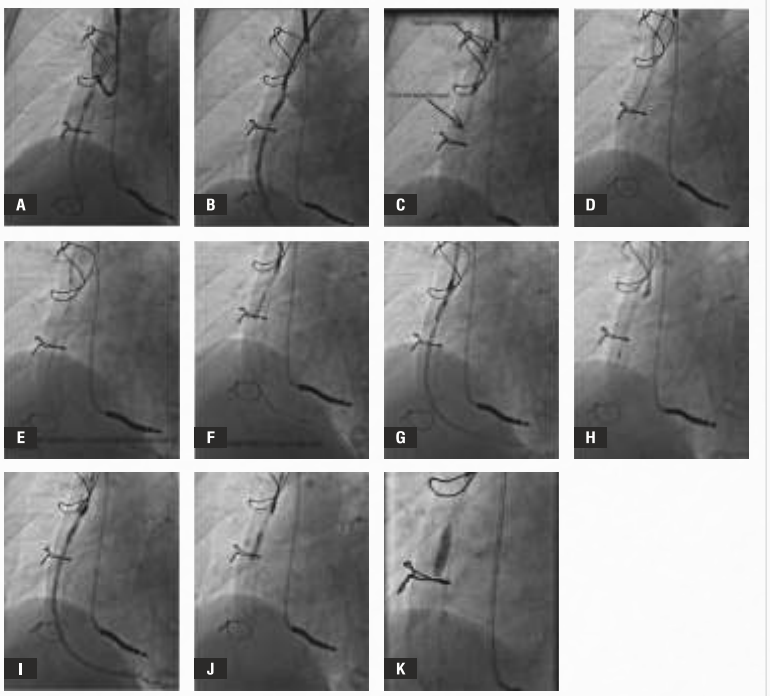
INTERVENTIONAL MANAGEMENT:

Procedural step:

Loading dose of antiplatelet was given. 7F Right Femoral Access was taken. Anticoagulation with unfractionated heparin as per weight of patient was administered. Initially 7F JR Guide catheter (Medtronic, USA) was used to cannulate the SVG graft but multiple attempts with it were futile. so 7F AL 1 Guide Catheter (Medtronic, USA) was used to cannulate SVG. However AL1 catheter could not be aligned to SVG graft. Wiring with workhorse Balanced Middleweight wire (Abbott Vascular, USA) was attempted by keeping the AL guide hanging near the ostium. But still wire could not be negotiated because of lack of support and lesion complexity. As the origin of SVG had downward take off, hard end of 0.035 inch guide wire was used to straighten the primary curve of AL1catheter and make the catheter downward looking.

With this maneuver we could get adequate support to cannulate SVG Graft and cross the lesion with Grand slam (ASAHI INTECC, Japan) PTCA wire. Gradual predilatation was done with 1.5 mm x 12 mm Traveler (Abbott Vascular, USA) balloon followed by predilatation with 2.0 mmx 12 mm Traveler (Abbott Vascular, USA) balloon. Hard end of Guide wire was removed after predilatation. Distal protection device FilterWire EZ (Boston Scientific, USA) could not be tracked across the lesion. So we planned to further predilate the lesion with 2.5mm x 12 mm Traveler (Abbott Vascular, USA) balloon, but it could not be tracked across the lesion. Hence Balanced Middleweight wire (Abbott Vascular, USA) was used as buddy wire for additional support, dilatation were given with semi compliant balloon 2.5mm x 12mm Traveler (Abbott Vascular, USA) balloon. However lesion did not give away. In view of undilatable lesion, IVUS was done with Otpicross 3.0F, 1mm x 135 cm, 40 MHz coronary imaging Catheter (Boston Scientific, USA), to profile lesion and for feasibility of Rota ablation. On IVUS Calcium was identified as very bright echoes. Nearly 360 degree Arc of superficial calcium with maximum thickness of 200 micron was evident. There was no evidence of any thrombus. Reference vessel diameter was 4-4.5 mm with evidence of extensive calcification in entire imaged SVG. Minimal luminal area was 3.8 sq.mm. Workhorse wire was replaced with floppy Rota wire 0.009inch, 330 cm over micro catheter FINECROSS MG 1.8F, 130 cm (Terumo, Japan), Rota ablation was done with 1.5 mm Rota Link burr (Boston Scientific, USA) @ 180000 rpm up to fall of 3000 rpm. Two runs with a polishing run of Rota ablation was given.

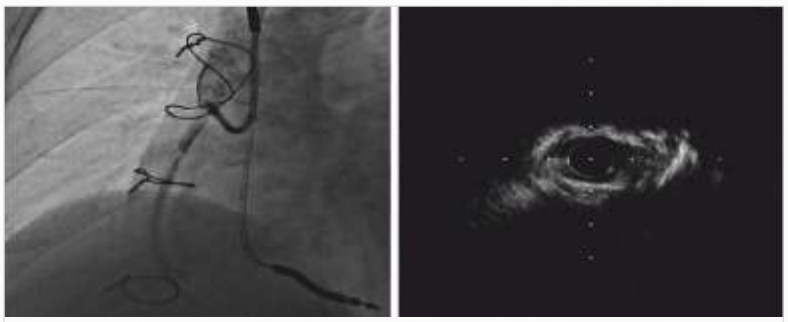
Rota wire was exchanged to workhorse wire over FINECROSS MG micro catheter. Micro catheter was removed using trapping balloon. Lesion was dilated with 3.5 x 12 mm NC Traveler (Abbott Vascular, USA) balloon at high pressure. Serial dilatation with 4.0 x 12 mm NC Traveler (Abbott Vascular, USA) balloon at high pressure. RESOLUTE ONYX (Medtronic, USA) 4.0 mm x 18mm stent was placed across the lesion and deployed at nominal pressure. Post dilatation with NC Traveler (Abbott Vascular, USA) 4.0 mm x 12 mm balloon and NC Traveler (Abbott Vascular, USA) 4.5 mm x 8 mm was done at High pressure, which gave angiographically good stent expansion. TIMI III flow without any complication could be achieved.



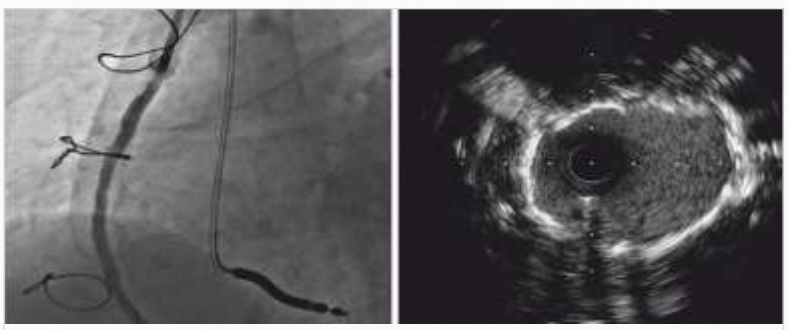
a) AL guide showing Proximal SVG lesion.

b) PTCA wire trying to cross the Lesion

c) Grand Slam wire across the lesion with Hardwire end of Guidewire opening the primary loop of AL Guide Catheter, d) Balloon Predilatation 1.5 mm x 12 mm balloon, e) FilterWire EX EPD could not cross the lesion, f) Buddy wire support with Balloon dilatation, g) Rota burr in SVG prior to Lesion site, h) Rota Burr pass across the Lesion Site, i) Stent 4.0 mm X 18mm Stent across the lesion, j) Post Dilatation with 4.0mm X 12mm NC balloon, k) Post Dilatation with 4.5mm X 8 mm NC balloon.



FIRST SHOOT & PRE ROTA IVUS



FINAL SHOOT WITH IVUS CORELATION

Management Issues:

1) Patient first needed medical stabilization in view of acute heart failure also for relief of angina
2) In view of patent LIMA to LAD and high risk for redo CABG in view of acute heart failure, advanced age and unstable patient with long standing diabetes PTCA of SVG was preferred. Native RCA had more complex appearing CTO lesion hence PCI to it was avoided.
3) Selecting proper Guide Catheter for adequate support is vital for ease and the success of the procedure. Here retrospectively MPA guide may have been a better choice, as we went ahead with the AL1 guide it needed maneuvering with the hard end of the guide wire for actual engagement.
4) In view of acute presentation of the patient with raised troponin and angiogram showing focal hypo dense shadow at the lesion site, we considered it to be likely soft lipid rich athero thrombotic lesion. Though there was tram-track calcification of the entire graft, dense calcification at the site of the lesion is relatively uncommon in SVG grafts. So we initially didn't consider undilatable calcified lesion as the primary case scenario.
5) Initial difficulty in passing the coronary wire and then during balloon dilatation prompted us to do IVUS imaging which made the lesion anatomy clear.
6) Though contraindicated otherwise for SVG, seeing the heavy calcification and old arterialized graft we carefully considered to go ahead with use of rota ablation ahead of other debulking devices like cutting/scoring balloon. Also passing the bulky devices like these across the lesion would not have been possible.

KEY LEARNING:

1) Proper study of coronary angiogram and Lesion analysis helps in planning the procedure.
2) Choosing proper guide catheter for adequate support is essential for smooth and uneventful procedure.
3) Hard end of Guide wire for can provide adequate support to proceed with procedure.
4) Stepwise approach to undilatable lesion is important. Graded balloon dilated helps in lesion dilatation and getting lesion access to bulking hardware.

Simple Techniques	Advanced Techniques
Adequate Guide Support	Cutting Balloon
Guide Catheter Extension	Rotational Atherectomy
Micro catheter support	Laser Angioplasty
Buddy wire technique	Intentional sub intimal techniques
Grenadoplasty	Intravascular Lithotripsy
	High Pressure Balloon

5) Imaging of vessel in undilatable lesion vessel gave important information for making decision of use of rota ablation, Calcium may mimic thrombotic appearing lesion on angiogram.
6) SVG grafts over a long period of time get calcified along with lesion calcification, Rota ablation of SVG graft can be done after adequate assessment of lesion.
7) Even after lesion preparation by rota ablation, and adequate dilatation with noncompliant balloon, High pressure post dilatation of the stent is important for proper stent expansion.

DISCUSSION:

Internal mammary artery, Radial artery and Great saphenous vein are the commonly used graft in Coronary Arterial bypass Graft surgery. As the graft ages chances of degeneration and graft failure increase especially more in venous graft. Veteran Affairs Randomized on /off Bypass study showed 11% LIMA and 23% Vein grafts failed at 1 year, At 10 year follow up patency rate of Arterial graft was 85% and 61% for venous graft.

In post CABG patients presenting as acute coronary syndrome over 70% of the times, culprit is SVG graft. SVG disease has thinner fibrous plaque, higher lipid burden, are softer and more friable. This increases chances of thrombus formation during PCI resulting in slow and no reflow phenomenon. Use of Embolic protection device is Class I recommendation during the PCI of SVG graft.

Veins have a thin media and a thick adventitia as opposed to coronary arteries which have media as the thickest layer and a very thin adventitia. Aortovenous grafting makes used vein, a high pressure conduit. As a result saphenous vein graft undergoes a process of arterializations which comprises of morphological changes in intima developing fibrous thickening, medial hypertrophy and lipid deposition. So SVG deteriorate faster than native coronary artery. Castagna et al showed calcium deposition in SVG occurs at average 10.5 years, whereas native coronary arteries take decades for calcium deposition. In the study SVG calcium was seen in 40% of the patient. Significant calcification occurs mainly within the wall (66%) and not within the plaque (33%), which suggests that SVG calcification is not just a result of lesion formation but also of wall changes associated with arterialization and degeneration. Where as in native coronary arteries lesion site calcium is present in 73% of the lesions and only reference site calcium is present in only 4% of the cases.

Sano et al studied the IVUS morphology of 15 aorto-ostial lesions and 60 lesions involving the shaft of the SVG. Among the 60 shaft lesions, 21 (35.0%) were proximal, 18 (30.0%) were mid, and 21 (35.0%) were distal. Shaft lesions more often contained soft plaque (p 0.02) and tended to have more ruptured plaques (p 0.1), Lesions located in the shaft of an SVG occurred in patients with diabetes and hypercholesterolemia, and had a larger plaque burden, more soft plaque, more plaque ruptures, and underwent positive remodeling more

QUALITATIVE IVUS ANALYSIS (Sano et al6)			
	Aorto-ostial Lesions (n=15)	Shaft Lesion (n=60)	p Value
Plaque composition			
Soft	4 (26.7%)	36 (60%)	0.02
Fibrous	6 (40%)	16 (26.7%)	0.3
mixed	5 (33.3%)	6 (10%)	0.02
Calcified	0(0%)	2 (3.3%)	0.5
Ruptured plaques	2 (13.3%)	21(35%)	0.1

In our case we experienced a very rare kind Proximal SVG lesion which had severe superficial calcification extending nearly 360 degree. This lesion had minimal lipid soft tissue contain.

SVG intervention has inferior outcome as compared to native vessel intervention, Graft interventions should be performed in patients with clear indication7. Knowledge of the Native vessel disease, Number of grafts, Type of grafts, age of the graft, and take off of the graft from aorta is important in selection of graft access and hardware selection.

JR or AL May be used if angle of origin is horizontal and in more steep inferior takeoff, MPA would be useful. Proper Guide selection eases procedure in terms of patient safety, reduction of procedural time, reduction in radiation exposure to interventionist and the team involved in the procedure.

In this case it was difficult to cannulate SVG initially with 7FJR 3.5 and then with 7F AL 1.0. AL guide could hardly engage and didn't give any support for wiring. So to make the AL guide coaxial by straightening the primary curve we used the hard end of 0.035 inch guide wire which was kept in till the wiring and predilatation could be completed. In view of thrombotic appearing lesion use of embolic protection device was planned.

Despite class I indication of using embolic protection device (EPD) in SVG PCI to reduce peri procedural Myocardial infarction, distal embolization and Slow-No Reflow4, EPD could not be negotiated across the lesion, even after predilatation.

In view of undilatable lesion we performed IVUS imaging which showed heavy superficially calcified lesion as well as extensive deep calcium in entire SVG. Heavy superficial calcium obscured the vessel anatomy and the deeper layers

were not visible. Post Rota ablation we did not used EPD as the lesion did not have any significant atherogenic plaque or thrombus

In view of thin layer of vein graft with risk of perforation and embolization of atherogenic soft plaque leading to increased slow /no reflow phenomenon, rota ablation of Venous Graft is contraindication as per manufacturer and guidelines do not recommend it.

There are very few case reports regarding use of rotational atheroctomy for undilatable SVG lesions with calcification. Mostly they are with respect to the lesions at the anastomotic site. Rota-ablation of shaft lesion of SVG is still rare.

Case report by Abhyankar et al8 for rotational Atherectomy of calcified Ostial saphenous vein Graft lesion, had a good follow up of 10month without any peri procedural complication and no restenosis.

Benrey et al9 treated 2 patient with rota ablation for highly localized calcified/ fibrotic lesions involving body of SVG, this was the first reported case for successful rotaablation in body of SVG.

Case series of 14 patients with 17 lesions reported by Thomas et al10 for Rotational Atherectomy involving SVG anastomotic lesions and distal native disease beyond it. Rota ablation was done for 4 Aorto-Ostial lesions, 10 distal anastomosis site lesions, 1 lesion in body of graft and 2 native vessel diseases. Although Thrombosis and distal embolization is a concern for SVG Rota ablation, was not seen.

Likewise during the procedure we did not experience any slow flow / No Reflow; however patient had prolonged hospital stay for recovery from heart failure post pci.

Another case report by Pelliano et al11 Showed use of rota ablation and delivery device like Guidezilla for stent delivery for difficult stent tracking scenario. As per our knowledge last reported case of SVG rota ablation was by Charbel et al12 for calcified non-dilatable, distal saphenous vein graft lesion.

This case of SVG PCI was challenging right from Catheter engagement to rota ablation of heavily calcified lesion with post dilatation of stent for giving a good procedural outcome.

IVUS imaging helped in proper assessment of lesion and provides vital information in decision making. Rota ablation can be used with safety in heavily Calcified arterialized SVG with low risk of slow / no reflow. Long term studies and data are need of time to evaluate utility of debulking devices in selected venous Graft lesions.

Case Study - 3

Case report | Open Access | Published: 19 October 2022

A rare cause of abdominal pain managed unconventionally: acute renal infarction caused by atrial fibrillation: a case report

Tao Ge, ZhengCai Zhu, Jinfeng Wang, Wenjiao Zhou, Evelyn J. Song & Shengxing Tang

Journal of Medical Case Reports 16, Article number: 381 (2022) | Cite this article

Abstract:

Background

Atrial fibrillation is one of the most common arrhythmias. The main thrombotic complication of arterial fibrillation is ischemic stroke, but it can also cause acute renal infarction from embolization. The low incidence and nonspecific clinical manifestations of acute renal infarction make it difficult to diagnose, often leading to either delayed diagnosis or misdiagnosis. Due to its rarity, more efficient treatment guidelines are helpful for the management of acute renal infarction related to the thromboembolic complication of arterial fibrillation.

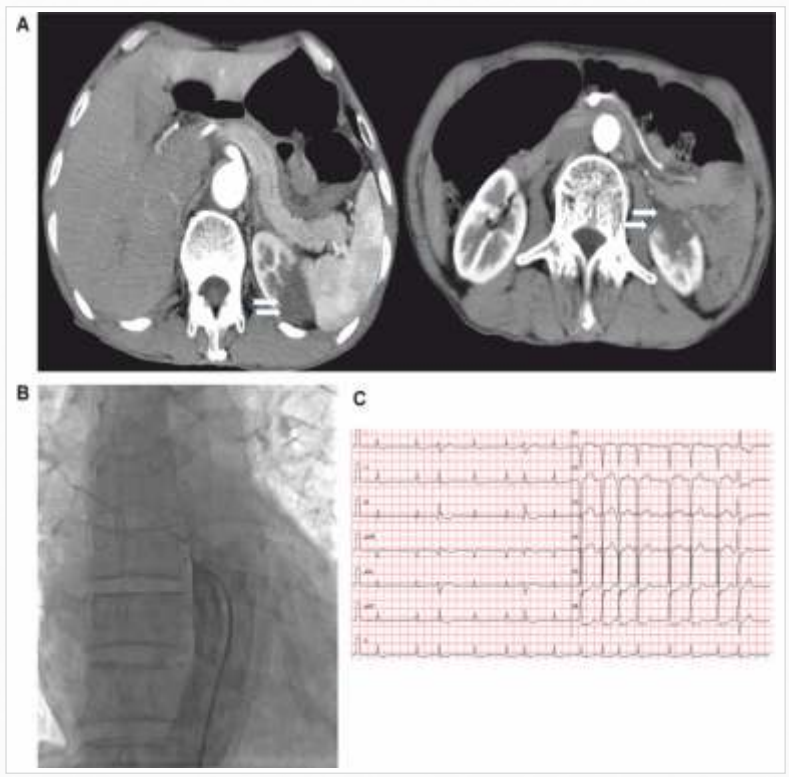
Case Description

The patient was a 66-year-old Chinese man with a past medical history significant for AF, not on anticoagulation per the patient's preference, and coronary artery disease (CAD) status post-percutaneous coronary intervention to left anterior descending artery about 1 year ago, currently on aspirin, clopidogrel, and rosuvastatin. He initially presented with 2 days of chest tightness, and acute coronary syndrome was ruled out. He then suddenly developed intermittent and sharp left-sided abdominal pain. Systemic review was negative for fever, chills, nausea, vomiting, diarrhea, or hematuria. He lives in a rural town working as a farmer, and is a current smoker with about 30 pack year smoking history. He denies any alcohol abuse or illicit drug use, and has no known drug allergies. Family history is non-contributory. Current home medications include aspirin (100mg), clopidogrel (75mg), rosuvastatin (10mg), furosemide (20mg), spironolactone (20mg), and isosorbide mononitrate (10mg). No known drug allergies were documented.

On admission, his vitals were normal, with blood pressure of 100/70 mmHg, heart rate of 68 beats/minute, and oral temperature of 36.3 °C. On examination, his heart rate was irregularly irregular without heart murmurs, jugular venous pressure (JVP) was normal, with no pitting edema in lower extremities. Lungs were clear on auscultation. His abdominal examination was notable for mild tenderness to palpation over the left quadrant without rebound or guarding. Bowel sounds were normal. The rest of the examination was unremarkable.

Routine laboratory tests showed normal complete blood count, liver function tests, amylase, lipase, and thyroid function tests. Creatinine was normal at 56 μmol/L (normal range, 40-130 μmol/L) with mildly elevated blood urea nitrogen (7.29 mmol/L [normal range, 2.3-7.1 mmol/L]). Urinalysis was negative for proteinuria, infection, and hematuria. Fecal occult blood test was negative. Both lactate dehydrogenase (LDH) and alpha-hydroxybutyrate dehydrogenase (α-HBDH) were elevated (283 U/l [normal range, 135-225 U/l] and 239 U/l [normal range, 76-195 U/l], respectively).

Bedside abdominal and renal vascular Doppler ultrasound were normal. Due to persistent abdominal pain of unclear etiology, a contrast-enhanced CT scan was then performed, revealing renal infarction of the left kidney (Fig. 1A). Coronary (data not shown) and aortic angiograms (Fig. 1B) were negative for coronary stenosis and aortic dissection. Given the CT findings and unresolved abdominal pain, a renal angiogram was performed and showed distal occlusion of both superior and inferior segments of the left renal artery (Fig. 2a). Next, attention was paid to the left renal artery. Two guide wires were introduced into the left renal superior and inferior segments (Fig. 2b), and the Pt wire was then passed through the distal end of the occluded superior artery. A 5 x 4 mm thrombus was aspirated by a suction catheter and locally inflated using a Maverick 1.5 × 15 mm balloon, and 0.1 mg nitroglycerin and 1 mg diltiazem



were injected through the microcatheter (Fig. 2c-g). Blood flow restoration to both superior and inferior segments of the renal artery and vessel potencies were confirmed by angiography after the aforementioned interventions (Fig. 2h), which is more clearly observed in the amplification of the images for renal angiograms after the surgery (Fig. 2k and l, arrow) compared with before the surgery (Fig. 2i and j, arrow). Abdominal symptoms resolved 6 hours after the operation. LDH (230 U/L) and α-HBDH (216 U/L) decreased and eventually normalized by postoperative day 5. He was continued on all home medications and started on warfarin post-procedure with an international normalized ratio

(INR) goal of 2-3. The patient was discharged on triple therapy with aspirin (100 mg), clopidogrel (75 mg), and warfarin (3.125 mg) for 1 month, followed by clopidogrel and warfarin for a further 6 months. At 6 months follow-up, the patient was symptom-free and renal function remained normal (creatinine 74 µmol/L [normal range, 57-111 µmol/L]). Repeat angiography was not performed at follow-up to avoid additional radiation exposure given low suspicion for persistent or recurrent renal infarction.

Rule Out:

In this case, our intervention quickly revascularized the occluded vessels, prevented permanent kidney damage, improved abdominal pain, and had minimal side effects. Local thrombus aspiration, balloon dilatation, and injection of vasodilators are not novel procedures, but the positive outcome in our case provides a promising new therapeutic intervention approach for AF-induced ARI while substantially reducing the risk of bleeding.

Additionally, laboratory tests are nonspecific in ARI. Previous reports suggested that elevation of LDH and C-reactive protein may be related to prognosis [16]. In our case, serum levels of LDH and α-HBDH were both elevated at the onset of symptoms and normalized after revascularization, suggesting that LDH and α-HBDH can potentially be used as markers for the diagnosis and treatment of ARI.

Conclusions

Acute renal infarction from thromboembolism is a rare but serious complication of arterial fibrillation. More efficient and different options for intervention methods will benefit the treatment of this disease. Here, we report a combination therapeutic method that has not been used in acute renal infarction associated with arterial fibrillation, and which restored renal perfusion and prevented long-term kidney injury.

Ref: https://jmedicalcasereports.biomedcentral.com/articles/10.1186/s13256-022-03608-z

Case Study - 4

Van Wyk-Grumbach Syndrome with Kocher-Debré-Sémélaigne Syndrome: Case Report of a Rare Association

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Abstract

Background: Van Wyk-Grumbach syndrome (VWGS) is a rare presentation of juvenile hypothyroidism which manifests in females as chronic autoimmune hypothyroidism, isosexual pseudoprecocious puberty, and multicystic ovaries. It uniquely presents with short stature and delayed bone age unlike other causes of precocious puberty. Kocher-DebréSémélaigne (KDSS) is a rare presentation of juvenile hypothyroidism manifesting as calf muscle pseudohypertrophy, delayed contraction and relaxation of reflexes, and percussion myxedema.

Objectives: To diagnose the rare association of VWGS and KDSS and to conduct a follow-up of the patient on replacement therapy.

Methods: We present a case of a 9-year-old female child who presented to the endocrine department with complaints of intermittent vaginal bleeding, short stature, and difficulty in walking. On evaluation she was found to be having autoimmune hypothyroidism, FSH-dominated isosexual pseudoprecocious puberty, delayed bone age, secondary pituitary macroadenoma, delayed relaxation of deep tendon reflexes, and pseudohypertrophy of calf muscles. The diagnosis of VWGS associated with KDSS was made. The patient was initially put on 25 µg thyroxine replacement, which was titrated accordingly, and was followed up after 6 months and 1 year.

Results: All the features of the syndrome improved after 12 months of adequate thyroxine replacement.

Conclusions: VWGS and KDSS are rare presentations of juvenile hypothyroidism, and their association is even rarer. Early diagnosis and prompt replacement therapy can avoid unnecessary investigations and surgical interventions.

Salient features of the case study:

- This is the second description of the simultaneous occurrence of these rare syndromes.
- VWGS is caused by a 'hormonal overlap in pituitary feedback' causing increased production of not only TSH but also prolactin, gonadotropins, and estradiol.
- Patient in the case had incomplete isosexual precocious puberty manifesting with menarche.
- The patient showed a typical hypothyroid facies with coarse features and puffiness along with dry brittle hair.
- Very high thyrotropin (TSH) and anti-thrombopoietin (TPO) antibody concentrations, along with a very low thyroxine (T4) concentration (TSH: 520 µIU/ml, T4: 12.87 nmol/l, anti-thyroid peroxidase antibodies: 1,300 IU/ml).
- Basal FSH, prolactin, and estradiol concentrations were significantly raised and were in the pubertal range, while LH was still prepubertal (FSH: 21.89 IU/l, LH: 0.05 IU/l, prolactin: 4.62 nmol/l, estradiol: 73.4 pmol/l), pointing towards the diagnosis of VWGS.
- In the patient, features like pseudohypertrophy of calf muscles, delayed relaxation of deep tendon reflexes, and percussion myxedema, along with raised serum CPK, point towards KDSS - another rare presentation of juvenile hypothyroidism.
- The unique features of isosexual precocious puberty caused by hypothyroidism is delayed bone age with growth retardation, despite the pubertal range of estradiol concentrations.
- Both VWGS and KDSS are easily reversible by early diagnosis and adequate thyroxine therapy.

Scan For Full PDF Case Study

HEALTHY LIVING

Physical activity in the afternoon linked to better control of blood sugar: Study

The current obesity pandemic is partially a consequence of lack of physical activity, and sedentary behaviour (prolonged sitting) during the day. Sedentary behaviour is associated with an increased risk of cardiometabolic diseases, including type 2 diabetes. Several studies have demonstrated that short breaks in sedentary time are associated with an improved cardiometabolic profile, including reduced triacylglycerol and glucose concentrations.

Findings from observational studies are supported by (semi-) experimental studies showing that frequent interruptions of prolonged sitting with standing or light activities resulted in improved glycaemic responses and triacylglycerol levels. High fasting serum triacylglycerol concentrations may reflect high liver

fat content, which is strongly associated with insulin resistance and ultimately preventing T2D.

Timing of physical activity is a relatively unexplored field in human biology and the mechanisms underlying the potential benefits of timing of physical activity remain unclear. Earlier studies have shown that metabolic responses to high-intensity exercise differed based on the time of day the exercise was performed. In addition, muscular strength as well as the metabolic function of skeletal muscle cells show a peak in the late afternoon, suggesting that being most active during this period may result in a more pronounced metabolic response than activity earlier in the day.

A new study published in Diabetologia (the journal of the European Association for the Study of Diabetes [EASD]) finds that afternoon or evening physical activity is associated with reduced insulin resistance (and thus better blood sugar control) when compared with an even distribution of physical activity through the day. Morning physical activity offered no advantages, concluded the study by Dr Jeroen van der Velde and colleagues at Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, the Netherlands.

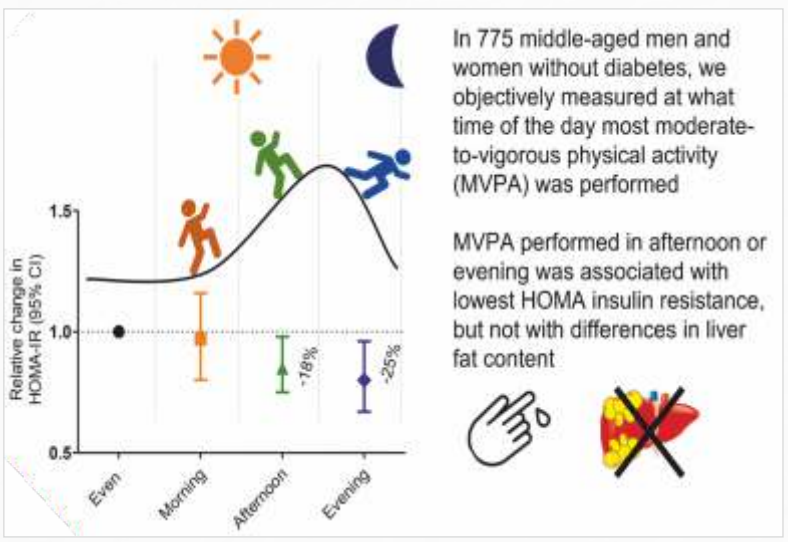
The researchers used data from the Netherlands Epidemiology of Obesity (NEO) study, a population-based prospective cohort study designed to investigate processes involved in the development of obesity-related diseases. Study participants were recruited between 2008 and 2012 with men and women living in the greater Leiden area being invited to participate if they were aged between 45 and 65 years and had a self-reported body mass index (BMI) of 27kg/m2 or higher. Invitations were also sent to all inhabitants aged between 45 and 65 years from one municipality within the region, as a reference population with a BMI representative of the general Netherlands population, resulting in a study population of 6,671 individuals.

Participants underwent a physical examination during which blood samples were taken to measure fasting and postprandial (after meal) blood glucose and insulin levels, while demographic, lifestyle and clinical information were obtained via questionnaire. They were also screened for suitability for an MRI scan, and roughly 35% of those able to undergo the procedure were randomly selected to have their liver fat content measured using this technique.

Recently, an association between morning bout-related moderate-tovigorous-physical activity (MVPA) and increased cardiovascular risk in men with type 2 diabetes, compared with later timing of MVPA, has been reported.

The researchers conclude "in addition to the total amount of daily MVPA, timing of MVPA during the day was associated with reduced insulin resistance: performing most MVPA in the afternoon or evening was associated with up to 25% reduced insulin resistance compared with an even distribution of MVPA during the day. These results suggest that timing of physical activity throughout the day is relevant for the beneficial effects of physical activity on inulin sensitivity. Further studies should assess whether timing of physical activity is indeed important for the occurrence of type 2 diabetes.

Reference: https://diabetologia-journal.org/wp-content/uploads/2022/10/van-der-Velde.pdf



FROM THE EDITOR'S DESK

Dear Doctor,

With the new year come new challenges and resolutions. And we, Apricans, are resolute in bringing forth novel medical and scientific information to you, our readers. It feels like yesterday when we started sending out this NCD newsletter to you, and now our newsletter has reached its 5th issue.

With every issue, we have taken baby steps and has nurtured this NCD issue by collecting the latest therapy and medical updates. The contributions made by various health care professionals in providing their challenging case studies is noteworthy and I thank all the authors for their significant contributions and hope for a continual support in the future.

With so much information out there, we, Apricans, aspire to provide evidence-based and unbiased medical information, and we want to get even better at meeting this standards. But this journey would be incomplete without your feedbacks and suggestions which can guide us to do better and to keep striving to deliver valuable information. Hence we urge you to start a dialogue with us at medical@aprican.com or ashitha.joseph@aprican.com or scan the QR code given to provide your recommendations about how our newsletter can be improved.

I hope this new year our association with you will grow stronger and profound.

Wishing you all a happy 2023.
May it be full of knowledge exchange and good fortune!

FEEDBACK

Please provide your feedback by scanning QR code

EDUCATE TO PROTECT

Aprica® Initiative

5000+

HCPs Enrolled
Personalized Education Material

Educate

More than 1 Lac patients Benefited
Aware complexity of NCDs

- One of the important factors in treatment of NCDs is “Education & Awareness”.
- We have taken many initiatives in this regard to spread message in the community about NCDs, its complications & treatment
- Non communicable diseases are increasing in India, result of unhealthy lifestyle choices.
- Aprica proudly introduced a Personalized Patient education material for creating an awareness that shines a spotlight on the devastating impact of NCDs on Health days.
- Under the banner of “Educate to protect” campaign we are taking an initiative for better access to quality NCDs education for people living with diabetes & Hypertension through leading clinicians.
- The core objective behind this campaign is to educate people by creating awareness regarding complexity of NCDs & underlying symptoms, risk factors, and treatment options.

To bring QOL in the Healthiest way possible

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