Title: Fundamental role of Warburg effect in various pathophysiological processes.

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ABSTRACT:

In this review article, the role of Warburg effect in various pathologies will be discussed using septic shock as the base model. I had proposed a slightly extended Warburg effect which I would like to call it as *'Warburg common pathogenesis model or Warburg differentiation dedifferentiation effect'*, which has the potential to explain septic shock and sepsis associated multi-organ dysfunction and many other major pathologies like SHT, PAH, CHF, DM, Asthma, ARDS, AKI implying most of the diseases may have a common pathogenesis as the underlying mechanism.

Increased Nitric oxide (NO) in sepsis via iNOS or any respiratory poison in general irreversibly inhibits the mitochondrial respiration and shifts the metabolic phenotype of the cell from oxidative phosphorylation (OXPHOS) to glycolytic phenotype and the change in metabolic phenotype is followed by the change in cell phenotype from the normal adult dynamic differentiation state to irreversible dedifferentiation states – embryonic phenotype, synthetic / proliferative phenotype, and cancer phenotype. This dedifferentiated state switching can be seen as the cells local survival strategy in response to injuries, but returning to their primitive forms leads to disorder and ends in global collapse of the organ systems and organism which requires order in terms of differentiation. Treatment in most of pathologies should aim at reversing Warburg effect by activation of mitochondrial respiration thereby decreasing the aerobic glycolysis and changing the cell to its normal adult dynamic differentiation phenotype i.e. all the drugs will be used here as differentiation therapy. Adrenergic blockers and Ascorbic acid may be the main treatment options, which are already used by some research groups, other options will be discussed in this article.

Even though high NO via iNOS was involved in most of the pathologies including sepsis, any substance that inhibits or uncouples the mitochondrial respiration can initiate this Warburg effect and irreversible dedifferentiation. A mild and reversible Warburg differentiation dedifferentiation effect may be necessary for normal functioning and the same effect in exaggerated and irreversible way leading to irreversible dedifferentiation states may be the underlying mechanism in most of the diseases including septic shock.

Keywords: Septic shock, Warburg effect, dedifferentiation, differentiation therapy, ascorbic acid, adrenergic blockers, glycolysis.

Abbreviations : systemic hypertension(SHT), pulmonary arterial hypertension (PAH),congestive heart failure (CHF), acute kidney injury(AKI),acute respiratory distress syndrome(ARDS),diabetes mellitus(DM),inducible nitric oxide synthase (iNOS) .

INTRODUCTION:

This review article tries to show the fundamental role played by Warburg effect in most of the pathologies. Warburg common pathogenesis model is proposed to show the common underlying mechanism in most of the pathologies and septic shock was used as the base model.

Sepsis is the harmful systemic response of the host to the infection (1). According to Lewis Thomas the host's response to pathogen is more detrimental than the pathogen itself (2). Septic shock and severe sepsis associated multi-organ dysfunction carries high mortality rate ~ 40 – 70% (3, 4). Septic shock is refractory to the vasopressors in most of the cases; this includes norepinephrine, the primary drug used in reviving blood pressure in septic shock. Vascular hypo reactivity to various vasopressors in septic shock has been studied extensively, many reviews are available (5, 86). Irrespective of advances in this field, exact underlying mechanism behind septic shock is still a mystery. Post mortem studies couldn't find the underlying cause in most of the cases, surprisingly most of the organs looked normal (6).Lot of treatment options which were successful in animal models were failed to show benefit in human studies, ranging from Nitric oxide Synthase (NOS) Inhibitors, Cyclooxygenase (COX) Inhibitors, endotoxin neutralizing proteins, TNF alpha antagonists etc.., (3). Some of the recent promising directions include, counterintuitive use of antihypertensive in septic shock – alpha2 adrenergic receptor agonists - clonidine (7-9), beta blockers reviewed in (10, 11) - aimed to reduce the sympathetic hyper activation and hyper metabolism associated with sepsis. Alpha2 AR antagonist also has been shown to improve survival in sepsis animal model (12). Vitamin C has been used in sepsis reviewed in (13), Glycolysis inhibitor shikonin (14), cytochrome C (15) and Caffeine (16).

Warburg common pathogenesis model has been proposed in this review article to explain the role of Warburg effect in most of the pathologies using septic shock as the base model. The model was built by slightly extending the 'Warburg effect', an extensively researched area in cancer biology, proposed by Otto Warburg in 1920's (17, 18). Warburg common pathogenesis model which will be discussed in the following section, not only explains septic shock and multi-organ dysfunction associated with severe sepsis, but explains most of the major medical problems like SHT, PAH, CHF, Asthma, ARDS, AKI. Cancer is not discussed here, as Warburg effect is an extensively researched topic in cancer field (19).Most of the supporting evidences were already done in the respective subfields, and this review article tries to show by putting the Warburg common pathogenesis model that there may be a common underlying mechanism in most of the pathologies. Also the same model in a mild and reversible way may be necessary for normal functioning.

THE HYPOTHESIS: WARBURG COMMON PATHOGENESIS MODEL OR WARBURG DIFFERENTIATION DEDIFFERENTIATION EFFECT (Figure 1):

In 1926 Warburg showed tumours relied on aerobic glycolysis metabolism (17). He extended the thoughts in his 1956 paper and showed that the cancer cells originate in two phases, 1.Irreversible inhibition of cell respiration - OXPHOS by agents like H2S, arsenious acid which he called respiratory poisons and this necessitates the cell to change to aerobic glycolysis metabolism for survival and proliferation, 2. This in turn causes a normal differentiated cell to change to a dedifferentiated cancer cell. He also suggested that there may be some cancer like states in between these 2 terminal states, which he called sleeping cancer cell states (18).Warburg effect is an extensively researched area in cancer biology, many excellent reviews are available (19).

Essentially Warburg told everything what is required for understanding septic shock 90 years back. A slightly extended Warburg effect was proposed in this review article (Figure 1),named as *'Warburg common pathogenesis model or Warburg differentiation dedifferentiation effect' may* explain most of the pathologies including septic shock. All the injuries to the cell can be divided into two types, 1.Injuries that increases OXPHOS e.g. inappropriate high energy food intake seen today in modern civilization and 2.Injuries that increase aerobic / anaerobic glycolysis e.g. Sepsis.

Injuries like increased NO in sepsis inhibits the mitochondrial respiration by inhibiting Cytochrome C oxidase enzyme in the electron transport chain and depending on the concentration of NO the inhibition can be reversible or irreversible (20-22). This switches the cells metabolic phenotype from OXPHOS to aerobic glycolysis (20), anaerobic glycolysis also included here as the endpoints may be same (19). Irreversible mitochondrial respiration inhibition by highly increased NO via iNOS is pathological whereas reversible inhibition by mildly increased NO via eNOS is physiological.In septic shock and most of the pathologies, these injuries lead to irreversible inhibition of cytochrome C oxidase and thus inhibition of mitochondrial respiration which triggers the metabolic phenotype change from OXPHOS to glycolysis. This metabolic phenotype change will be followed by switching of the cells phenotype from normal adult dynamic differentiated state to irreversible dedifferentiation states – embryonic phenotype, synthetic / proliferative phenotype and cancer phenotype.Injuries that increase OXPHOS leads to irreversible differentiated state, where the cells have two options to proceed further 1.first path leads to apoptosis, may be due to increased cytochrome C release and 2.the second path may lead to the inhibition of mitochondrial respiration and switching to glycolytic phenotype / irreversible dedifferentiation phenotype for survival.

When the mitochondrial respiration is inhibited for example by NO, the electron flux will be stopped, the energy need will be met by the glycolysis and the glycolytic ATP move to the mitochondrial matrix, which makes the ATP synthase to work in reverse way i.e. ATP hydrolysis

instead of synthesis and pumps the proton from the mitochondrial matrix to the outer aspect of the inner membrane, all this will result in mitochondrial membrane hyperpolarization (20).It has been already shown mitochondrial membrane depolarization lead to cytochrome C release and apoptosis (23)and mitochondrial hyperpolarization is related to cancer state (24), the mitochondrial membrane hyperpolarization may inhibit the release of cytochrome C. This along with Hypoxia inducible factor 1 alpha (HIF 1alpha) stabilization due to mitochondrial inhibition by NO may lead to antiapoptosis and survival (20,25).

But why the cells have to switch to the irreversible dedifferentiation, because this may be the local survival strategy of the cells under the circumstances of injury. These primitive irreversible dedifferentiated states may have survival advantage over the differentiated states. What happens in pathologies like sepsis is this local survival strategy of the cells to return to their primitive dedifferentiated states results in global order collapse in organ systems and organism, for the organ systems to function properly needs ordered state in terms of differentiation.

Even though in normal state, the cell is in adult dynamic differentiation state with predominant OXPHOS, there are exceptions to it, where some cells in some organ systems may already be in mild Warburg dedifferention state with increased glycolysis to survive in the harsh environment they live and it may be necessary for its normal function e.g. Podocytes in renal system (167).

The same Warburg common pathogenesis model in a mild and reversible way may be necessary for managing day to day minor injuries and for other normal functions. If a minor injury happens, the cells switch from its normal adult dynamic differentiated state to reversible Warburg dedifferentiated state and after responding to the injury by surviving and proliferation, the cells return back to their normal adult dynamic differentiated state. This kind of approach has been already shown for example in renal system (161).Considering the potential role played by the mild and reversible Warburg common pathogenesis model in normal functioning, it would be more appropriate to call it as '*Warburg differentiation dedifferentiation effect*'**.**

What happens in sepsis and in major medical problems like SHT, PAH, CHF, DM, AKI, Asthma, ARDS - is the cells in the specific organ system may exhibit Warburg effect with the metabolic phenotype shift to glycolytic phenotype and cellular phenotype shift to irreversible dedifferentiated states. Irreversible term is used here in the sense that it is very difficult to return back to normal adult dynamic differentiated state. In short, Warburg differentiation dedifferentiation effect in a mild and reversible way is necessary for normal functioning and exaggerated irreversible way leads to various pathologies.

WARBURG COMMON PATHOGENESIS MODEL IN SEPSIS (Figure 2):

In sepsis, lipopolysaccharide (LPS) acting through toll like receptor (TLR4) activate NFkB (1) leading to activation of iNOS and increased NO (26). Through TLR4 LPS also lead to production of

cytokines (1, 27). Cytokines in turn again acts on NFkB to activate iNOS thus amplifying the NO production (28, 29).These pathways may involve MAPK and calcium independent PKC isoforms (26). It is well known that the catecholamines in the plasma were increased in sepsis (30, 31). Even though other factors like Renin Angiotensin Aldosterone System(RAAS) (32), Cyclooxygenase pathway (33) also involved and their activity is increased in sepsis, I will focus here only on sympathetic hyper activation.

In spite of increased catecholamine level is sepsis; it seems odd to give exogenous catecholamines like norepinephrine for the treatment in septic shock. Many had already pointed out catecholamine treatment carries risk in treating shock (30, 34). In fact adrenergic blockers are already used long time back in shock states in animals and in patients (10,11,30,35,36).We will see more about this aspect in vascular dysfunction section.

It is already known that the alpha1, beta2 adrenergic receptor activation can lead to eNOS activation and NO production, this pathway involves Akt (37 - 39).Norepinephrine has been shown to enhance cytokine induced in iNOS, this pathway involves alpha, beta adrenergic receptors and MAPK(40). From the above evidences one can see usually adrenergic receptors activation at basal level may lead to mild eNOS activation and this pathway seems to involve PI3K/Akt and MAPK.

Adrenergic receptor hyper activation during sepsis due to increased catecholamines may cause hyperactivation of eNOS, this has been shown already in relation to the early hypotension seen in the biphasic vascular response in sepsis (41, 42). Adrenergic hyperactivation and cytokines like TNF alpha , IFN gamma and toxins in sepsis -LPS, all acting through PI3K / Akt /mTOR and MAPK may lead to eNOS hyperactivation initially and ends up in eNOS uncoupling and iNOS activation and the late hypotension seen in the biphasic response in sepsis was already shown to be related to iNOS activation (41, 42).

Nitric oxide role in septic shock is an extensively researched area, reviewed in (43, 44). An early hypotension and late hypotension has been already shown in sepsis, initial phase is considered to be due to increased eNOS activity and late hypotension is considered to be due to iNOS action (41, 42).Inhibition of iNOS has been tried as a treatment option for shock ,eventhough NOS inhibitors were successful in animal studies, TRIUMPH trial conducted using nonspecific NOS inhibitor tilarginine in cardiogenic shock in humans didn't showed beneficial effect, also it showed it may be harmful (45). Many thought the reason for failure may be due to the nonspecific inhibition of NOS and selective iNOS inhibition with eNOS restoration may be beneficial (46, 47).

As discussed in the previous section, very high NO concentration in sepsis leads to irreversible inhibition of the mitochondrial respiration has been known already (20,21,48,49).This may lead to HIF1 alpha stabilization and activation of glycolytic enzymes (20, 50). It is known already that the aerobic glycolysis lead to formation of glycolytic ATP, which moves from the cytosol to

mitochondrial matrix and makes the ATP synthase to work in reverse mode and hydrolyse the glycolytic ATP and pumps the protons from matrix to inner mitochondrial membrane leading to mitochondrial hyperpolarization (20). Mitochondrial depolarization has been shown to lead to cytochrome C release and thus initiates apoptosis (23). Mitochondrial hyperpolarization has been related to cancer (24),may be through inhibiting the cytochrome C release, which along with HIF 1 alpha stabilization leads to the inhibition of apoptosis (20).

Fink had already showed the inhibition of mitochondrial respiration in sepsis and suggested this may be the underlying cause for multi organ dysfunction in sepsis (21). Geng et al showed cytokine induced NO inhibits mitochondrial respiration in VSMC (51). Interestingly treatments focussed on activating the cytochrome C oxidase in animal models of sepsis has been already shown, cytochrome C has been given exogenously to overcome the mitochondrial inhibition in sepsis animal model showed increased cytochrome C oxidase activity and improved the survival (15). Caffeine treatment in the sepsis model also showed similar findings (16) and same team by suggested that the mitochondrial respiration inhibition in sepsis can be seen as a adaptive response and suggested similar to Fink that this mitochondrial dysfunction may be the underlying cause for multi organ dysfunction in sepsis (52, 53).

Lactic acidosis in septic shock – the Key: Lactic acidosis happens in septic shock is well known and many thought it could be used as a prognostic indicator (54).Traditionally lactic acidosis in septic shock and in other pathologies are thought to be due to hypoxia as a result of anaerobic metabolism. But many showed this may not be the case and pointed out that lactic acidosis in septic shock may be due to aerobic glycolysis (22, 55 - 58).Yang et al showed using shikonin that the inhibition of aerobic glycolysis could be used as an treatment option for septic shock and linked the aerobic glycolysis to Warburg effect, but they focussed only on the aerobic glycolysis aspect not on the cell phenotype changes (14). Many works on using Dicholoroacetate (DCA) to treat the lactic acidosis in sepsis can be seen in this context (58, 59).It has been already shown that DCA can be used for reversal of Warburg effect in cancer (60).

Endotoxin has been already shown to increase glycolysis in animal sepsis model and adrenergic system plays a role in it was shown by blocking it with alpha + beta adrenergic blockers (61) and it was also shown to be reduced by ouabain (62) . Adrenergic receptors (ARs) are already shown to be involved in glycolysis and lactate production and involve sodium potassium ATPase (36, 55, 63, 64). Interestingly Bruno levy et al showed beta 2 ARs are involved in lactate production in shock and showed beta blocker, Ouabain reduced this (55) and Luchette et al used combined alpha + beta blocker to reduce the lactate in haemorrhagic shock (36).In short, many studies in septic shock already showed - NO inhibition of mitochondrial respiration, aerobic glycolysis, use of glycolytic blockers ,adrenergic blockers, and cytochrome C oxidase activators (7-11, 14-16, 20-22, 65). The

stage is already set. In spite of all this a full application of Warburg effect including cell phenotype change to solve the septic shock mystery has not been done seems to be surprising.

In septic shock the high NO via iNOS activation irreversibly inhibits mitochondrial respiration which changes the metabolic phenotype change from OXPHOS to glycolysis and this may be followed by cell phenotype change from normal adult dynamic differentiation state to irreversible dedifferentiation states similar to cancer phenotype change in Warburg effect (Figure2). Irreversible dedifferentiation has at least 2 states – embryonic state and synthetic or proliferative state. These states are equivalent to the sleeping cancer states as mentioned by the great Warburg (18).

Cell type change to embryonic dedifferentiated state may express the properties that they system specific cells expressed during their foetal or neonatal state, for example Vascular smooth muscles (VSM) have beta 2 adrenergic receptors as their predominant receptors in the foetal pulmonary and aortic VSM, and alpha1 adrenergic receptors which were low in foetal state compared to the adult pulmonary and aortic VSM, tends to increase during the developmental maturation (66).

Cell type change to synthetic / proliferative dedifferentiated state is associated with proliferation of cells with loss of contractile apparatus, for example VSMC phenotype changes has been shown long back, and the change from contractile to synthetic / proliferative phenotype leads to loss of contractile apparatus and it has been already suggested that these changes may be the underlying cause in various vascular pathologies (67). VSMC proliferation / dedifferentiation have been already related to various pathologies and this change has been related to Warburg effect (68).

These changes to irreversible dedifferentiation state may be accompanied by changes in the ion channels, with many types of ion channels it seems to be difficult to identify which ion channels are changed or expressed in these states. But there is a simple solution for it if we take the guide that the cancer cells have depolarized cell membrane potential (69).All the changes in the ion channels during irreversible dedifferentiated states in many pathologies like septic shock tend to move towards the depolarized cell membrane potential. For example, L type calcium channels in contractile VSMC has been shown to be lost on switching to synthetic /Proliferative phenotype and increased expression of transient receptor potential channels (TRP) has been shown (70, 71).Spontaneously hypertensive rat (SHR) model VSMC synthetic type were already shown to be more depolarized when compared to the normal wild type counterpart and the depolarized state of the cell has been related to proliferation (72).

DURING INJURY ALL THE CELLS IN AN ORGAN SYSTEM MOVE TOWARDS A COMMON CELL TYPE WHICH HAS BETTER SURVIVAL ADVANTAGE (Figure 4):

In most pathology, each organ systems specific cell types may tend to move towards one dedifferentiated cell phenotype that has the better survival advantage and proliferation. For

example, in septic shock all the cells in the vascular system – Vascular endothelial cells , Vascular smooth muscle cells (contractile phenotype), fibroblasts all tend towards Vascular Smooth muscle cell (synthetic / proliferative phenotype), Figure 4. This kind of phenotype change has been shown already in atherosclerosis (73-75) and asthma (76).Vascular endothelial cells by endothelial to mesenchymal transition change to VSMC (Synthetic/ proliferative) phenotype, VSMC (contractile) by phenotype change switch over to its synthetic/ proliferative type and fibroblasts switch to myofibroblasts which has features similar to VSMC (synthetic /proliferative) phenotype but are hyper contractile. In spirit of aerobic glycolysis / proliferation happening in these states i will call these states as Warburg irreversible dedifferentiation states (68, 77).

ASCORBIC ACID AND PHENOTYPE CHANGE (Figure 5):

But what triggers this cell phenotype change apart from the glycolysis shift? One possibility is that the decreased ascorbate level in the body has the potential to induce phenotype change, Figure 5. Cameron et al thought endothelial dysfunction and the problem in ECM production by ascorbic acid may lead to cancer (78). It is well known that ascorbate is the one of the key substrate used to activate cytochrome C oxidase (51) has to be seen in this context and ascorbate deficiency may lead to respiratory dysfunction has been suggested long back (78).As seen earlier increased NO in sepsis inhibits mitochondrial respiration and triggers glycolytic phenotype change. Ascorbic acid level has been shown to be decreased in sepsis (79). Ascorbate level may be decreased due to increased scavenging that might have occurred in these conditions. Ascorbic acid is essential for extracellular matrix production (ECM). Serum heparan sulfate level has been shown to be elevated in sepsis (80). Serum hyaluronan, syndecan were also shown to be decreased in sepsis (81).Nelson et al showed increased glycosaminoglycans (GAG) in septic shock and related this to endothelial damage (82). All these evidence shows endothelial glycocalyx degradation and endothelial dysfunction in sepsis. Ascorbic acid role in the synthesis of GAG has been shown long back (78). It has been already shown that the removal of heparan sulfate from the cell surface may trigger phenotype change in vascular smooth muscle (67).Increased degrees of movement of a cell may trigger cancer phenotype change (83). On the whole, decreased ascorbate may lead to failure in regulation of mitochondrial respiration activation, decreased ECM regulation and endothelial dysfunction which may increase the degree of movement of the cells and trigger phenotype change (78).

EXPLAINING VASCULAR DYSFUNCTION IN SEPTIC SHOCK USING WARURG COMMMON PATHOGENESIS MODEL (Figure 3):

Normally catecholmines act on adrenergic receptors in VSMC, which are G protein coupled

receptors (GPCR) and this in turn leads to G alpha subunit activation of the following 3 pathways to cause vasocontraction 1. Inositol triphosphate (IP3)/Calcium pathway, leads to increase in intracellular calcium level and activate myosin light chain kinase (MLCK) to phosphorylate Myosin light chain to produce vasocontraction 2. Diacylglycerol (DAG) – protein kinase C (PKC) and 3.RhoA/Rho Kinase pathway, both these pathways inhibit Myosin Light chain phosphatase (MLCP) and produce vasocontraction (5, 84). As we had seen earlier septic shock induced hypotension is refractory to vasopressor agents including the first choice drug norepinephrine (5).As discussed earlier, biphasic hypotension has been shown in sepsis – early hypotension is considered to be due to increased eNOS activity and late hypotension is to considered to be due to iNOS action(41, 42). Some of the possibilites already explored in understanding the vascular hypo reactivity in sepsis include, NO induced alteration in alpha1 adrenergic receptors by peroxynitrite (85) ,inhibition of RhoA/Rhok (41), PKC agonist improved the vascular hypo reactivity showed the involvement of PKC in this, also MAPK seems to be activated in shock and NO could activate KATP and K_{ca} channels leading to hyperpolarization, adrenergic receptor desensitization , cyclooxygenase (COX) pathway involvement by COX2 activation etc may be some of the reasons for vascular hypo reactivity are reviewed by many (5,86). Many treatment options which were successful in septic shock animal models failed in human studies. Failure of nonspecific NOS inhibitors in septic shock, activated protein C are few examples (3).

It has been already shown adrenergic receptor activation through G beta gamma subunit activates PI3K/Akt and MAPK pathways, may involve calcium independent PKC isoforms (40, 87-90) and finally may hyperactivate eNOS (37). It is interesting in this aspect to see beta 2 receptors action which normally by Gs alpha subunit lead to protein kinase A (PKA) activity, has been shown by Daaka et al to phosphorylate the beta receptor and switch over to its activity through G beta gamma subunit pathway to MAPK (91). Also adrenergic activation of glycolysis is well known (55, 63, 64).Overall the adrenergic Receptor activated G subunit beta gamma mediated pathway through PI3K /Akt and MAPK lead to eNOS activation and glycolysis but mildly under normal activation. During adrenergic hyper activation this pathway may lead to hyper activation of eNOS and increased glycolysis as shown above. The increased NO inhibits the mitochondrial respiration reversibly and leading to increased reactive species, and the reactive species may oxidize the tetrahydrobiopterin (BH4) resulting in eNOS uncoupling (92, 93).

From the above evidences we can see that the adrenergic pathway hyper activation along with cytokine and LPS activate iNOS leading to very high NO. Usually a very high NO occurs through iNOS like in sepsis but in some cases like anaphylaxis it may happen through eNOS itself (94). What matters is the high NO level, it doesn't matter which way it comes through as rightly pointed out by Lowenstein et al (95). High NO in sepsis due to iNOS activation (5), as shown above

inhibits the mitochondrial respiration irreversibly (20,21,48,49).

With this background we can see that the Warburg common pathogenesis model may be the underlying mechanism behind the septic shock. The high NO level in sepsis irreversibly inhibits the mitochondrial respiration in vascular smooth muscle cell (VSMC) and shifts the cell to change its metabolic phenotype from OXPHOS to glycolysis and this in turn may be followed by a change in cell phenotype from the normal adult dynamic differentiated state to irreversible dedifferentiation states initially to VSMC embryonic state and later to VSMC synthetic / proliferative state(Figure 3). Also all the key cells in the vascular system tend to move towards the VSMC synthetic / proliferative phenotype which may have better survival advantage as discussed above (Figure 4). Decreased ascorbate level in sepsis may play a key role in this phenotype change as discussed above (Fig 5).

There may be at least 2 stages in this septic shock progression (Figure 3). **A.** The initial state occurs when the cell phenotype is in its normal adult dynamic differentiated state. Adrenergic hyper activation through G beta gamma subunit activated pathways as seen earlier lead to eNOS hyper activation and finally ends in eNOS uncoupling.As already shown by many increased nitric oxide leads to the inhibition of – IP3 /calcium pathway, DAG calcium dependent PKC isoform pathway and RhoA/ Rhok pathway, it is interesting to see that all of these are G alpha subunit mediated pathways. The net result is exogenous or endogenous catecholamines may cause 1. Decreased vasocontraction due to inhibition of IP3/ calcium pathway or 2. Paradoxical vasorelaxtion due to inhibition of PKC and RhoA/RhoK pathway.**B.** As shown earlier adrenergic hyperactivation may act through G beta gamma subunit and activates PI3K/Akt , MAPK pathways, this may involve calcium independent PKC isoforms (40,87-90) and all this finally lead to eNOS hyperactivation (37), then eNOS uncoupling (92),(93) and iNOS activation (41,42). iNOS activation also occurs through Cytokines and LPS as shown earlier (40,41). eNOS uncoupling and iNOS activation will lead to very high nitric oxide level and this as seen earlier irreversibly inhibits the mitochondrial respiration at cytochrome C oxidase and shifts the cells metabolic phenotype from OXPHOS to glycolysis and followed by change in cell phenotype from its normal adult dynamic differentiated state to irreversible dedifferentiated states initially to embryonic state and then to synthetic / proliferative state.

1.VSMC Embryonic dedifferentiated state (Figure 3):When the VSMC are in this state, there may be a change in adrenergic receptor expression by VSMC and the cells may have beta2 AR as the predominant receptors like it was in fetal state (66).

Paradoxical vascular responses to Norepinehrine and acetylcholine: Exogenous / endogenous catecholamines given when the VSMC are in embryonic state in septic shock may produce paradoxical vasorelaxation. It is interesting to see noradrenaline induced vasorelaxation in neonatal

arteries in this context (96) where VSMC are expected to be in embryonic dedifferentiated state expressing beta 2 AR as the predominant ARs. It is interesting to see that the norepinephrine induced vasodilation in the isolated coronary arterioles of heart failure patients in this context, where the VSMC are expected to be in dedifferentiated state (97).Also at this point the endothelial dysfunction might have happened as all the cells in the vascular system tend to move towards VSMC synthetic/ proliferative type. In this state like the paradoxical response of norepinephrine , one can expect acetylcholine may also produce paradoxical response of vasocontraction instead of its usual vasodilation, which is indeed the case as shown in LPS model (98), in atherosclerotic coronary artery (99), in PAH (100). Also it has been shown that this paradoxical vasoconstriction by acetylcholine was associated with high mortality (101).

2. VSMC synthetic / proliferative dedifferentiated state (Figure 3): This state may be further divided into acute phase and chronic phase. In acute phase, the cells contractile apparatus may be decreased due to the VSMC phenotype change. As shown earlier, VSMC contractile phenotype to VSMC synthetic / proliferative phenotype show decreased contractile apparatus (67). In this state the vascular response to exogenous / endogenous catecholamines may produce paradoxical vasorelaxation. In chronic phase, the vascular tone may be increased due to increased VSMC proliferation or hyper contractile due to the presence of myofibroblasts. This chronic phase may be seen as an equivalent to systemic hypertension (SHT) and pulmonary arterial hypertension (PAH), which will be explained later.

Treatment options for septic shock: Many of the treatment options mentioned below were already tried in sepsis but failed to understand the full significance of it. In this section, the focus will be only on adrenergic blockers. Other treatment options will be explored later including the key drug ascorbic acid. Treatments were proposed here as differentiation therapy.1. In the first state when the cells are in normal adult dynamic differentiated state: As alpha1 ARs are the predominant receptors in VSMC in adult state (66), alpha 1 blockers like prazosin may be a better choice than beta blockers, combined alpha + beta blockers may work well.2. When the cells are in irreversible dedifferentiated states (embryonic and synthetic /proliferative state): As the cells were gone back to their primitive states and beta2 ARs are the predominant receptors in VSMCs in this foetal state (66). Beta blockers may be a better choice than alpha blockers at this stage. Again combined alpha beta blockers may work well. As discussed earlier, catecholamine treatment in septic shock may do harm rather than saving the patient (30, 34). Adrenergic blockade in septic shock has been tried long back; where beta blocker was used (35).Adrenergic blockers were used in haemorrhagic shock to reduce lactate level, where combined alpha and beta blocker reduced the lactate level (36). It is interesting to see the use of prazosin in treating scorpion sting in this context (102).Many recent

advances in septic shock include the counterintuitive use of antihypertensive in septic shock (8). Alpha 2 agonist Clonidine has been shown to reduce the sympathetic hyper activation in septic shock has been shown (7, 9) alpha 2 adrenergic blocker Yohimbine has been used in sepsis model (103), beta blocker Esmolol improved the cardiac dysfunction in sepsis model can be seen in this context (104). Use of beta blockers in sepsis (11) is waiting for a systematic review (105).Beta blockers and alpha blockers were used in different conditions to reduce the cell proliferation can be seen in this context (106 - 108).Cyclooxygenase pathway activation and increased RAAS activity in sepsis also seem to work in the same way as adrenergic hyper activation (32, 33). But cholinergic pathway seems to work in a opposite way in sepsis. Cholinergic agonists increased the survival in experimental sepsis (109) and vagal nerve stimulation (VNS) prevented the shock in sepsis model (110).

EXPLAINING MULTI ORGAN DYSFUNCTION IN SEPSIS AND EQUIVALENT KEY DISEASES USING WARBURG COMMON PATHOGENISIS MODEL:

Various other pathologies may also be explained using this Warburg common pathogenesis model by explaining the multi-organ dysfunction in sepsis. Most of the supporting evidences were already shown and in some pathologies it is already linked to Warburg effect for example in PAH (111).

***Sytemic Hypertension (SHT)*:** It is well known that VSMC proliferation occurs in hypertension (112, 113). VSMC phenotypic switching has been known for long time (67), and shown to play a crucial role in various vascular pathologies (114,115).It is surprising to see warburg effect was not used to explain SHT. Warburg common pathogenesis model may explain SHT. All the events which were mentioned for vascular dysfunction in sepsis except the triggering event seems to underlie in the evolution of SHT, and SHT may be equivalent to the chronic phase of irreversible dedifferentiated state of VSMC seen in Figure 3. The triggering injury for SHT include many possibilities like stressful life leading to sympathetic hyper activation, high energy food intake etc. Nifidipine one of main drug used in the treatment of SHT, has been shown to inhibit dedifferentiation of VSMC by inhibiting Akt can be seen in this context (116). All the antihypertensive drugs mode of function can be seen in this context as differentiation therapy including adrenergic blockers. Retinoic acid has been shown to inhibit VSMC proliferation (117) has to be seen in this context.

***Pulmonary Arterial Hypertension (PAH)*:** Surprisingly unlike SHT, the pathogenesis of PAH has been already linked to Warburg effect , including metabolic phenotype change , pulmonary artery SMC proliferation, HIF 1alpha activation, hyperpolarized mitochondrial potential in pulmonary artery SMC in PAH has been shown already(111,118,119). All Trans retinoic acid (ATRA) has been shown to be decreased in idiopathic PAH, and ATRA could be a potential therapy for this

patients has been shown already (120). ATRA is used here as a differentiation therapy.

Atherosclerosis: Vascular proliferation and VSMC phenotype change to synthetic / proliferative type has been already explored in atherosclerosis (73, 115). Statins are one of the standard drugs used in this condition; if the atherosclerosis and septic shock has common underlying pathogenesis then one can expect statins may also work in septic shock. Indeed it has been already shown that the statins reduced the vascular hypo reactivity in animal sepsis model (121, 122).

***Cardiac dysfunction in sepsis and Congestive heart failure*:** Cardiac dysfunction in sepsis and congestive heart failure (CHF) can be explained by Warburg common pathogenesis model (Figure 1 and 2).Except the injuries that trigger the cardiac dysfunction in sepsis and CHF may be different, all the other events are same for both. Injuries that trigger the CHF are many e.g. stressful life, sedentary life style, and high energy food intake. In both cases the cardiomyocytes change their metabolic phenotype from OXPHOS to glycolytic state and this may be followed by a change in cell phenotype from the normal adult dynamic differentiated state to the primitive irreversible dedifferentiated states – embryonic state and synthetic /proliferative state which results in decreased contractility and decreased cardiac output. Increased sympathetic activity has been shown in CHF(123 - 125). Decreased eNOS and iNOS activation has been shown in heart failure (126 - 128). Mitochondrial respiration has been modified in heart failure; OXPHOS is decreased with increase in glycolysis (129). Also adrenergic receptors states were changed in CHF, where beta 1 ARs are decreased with increase in beta2 ARs and increased G Protein receptor kinase which lead to beta receptor uncoupling (125,128,130,131). Myosin light and heavy chains are changed to their foetal isoform in CHF (128).All these findings support the Warburg common pathogenesis model's role in CHF.Early cardiac development has been shown to be associated with glycolysis which helps in proliferation of cardiomyocytes and increased mitochondrial OXPHOS occurs during cardiac maturation to adult state and adult heart may switch to it foetal metabolic phenotype i.e. glycolysis under the conditions of stress (132). Adult cardiomyocytes during dedifferentiation express increased GLUT1 and decreased GLUT 4 leading to insulin resistance has been shown already (133), and Akt plays a role in this insulin resistance (134). It has been shown that the NO in cardiomyocytes induce HIF 1 alpha to produce VEGF and angiogenesis involves PI3K/Akt pathway (25). Richard levy et al already showed glycolysis in septic animal model and suggested cytochrome C oxidase inhibition in this condition as an adaptive response and this may be the cause for other organ dysfunctions also in sepsis (52, 53). By activating cytochrome C oxidase by caffeine and cytochrome C in animal sepsis model the same team showed this could be used as treatment in sepsis (15, 16).

Ion channel expression change during dedifferentiated state as mentioned before can be expected to happen in cardiomyocytes. It has been shown already, cultured cardiomyocytes on dedifferentiation

express a nonselective cation channel(135).Decreased L type calcium channels in failing heart myocytes has been shown(136), one can relate this to the decrease in L type Calcium channels in dedifferentiated VSMC as discussed above (70,71). Late component of sodium current has been shown to be increased in failing heart, increased intracellular sodium as a result of this makes the sodium/calcium exchanger (NCX) to work in reverse mode and results in increased intracellular calcium (137).It has been shown intracellular sodium was increased and this leads to increased calcium in cardiomyocytes in heart failure(138,139).

Cardiac glycosides are used in the heart failure treatment shown to improve contractility by inhibiting the sodium potassium ATPase. But it is difficult to see from the above evidences why the inhibition of the sodium potassium ATPase which leads to increase in intracellular sodium should work in heart failure, as the cells were already loaded with increased intracellular sodium and calcium. It looks like in heart failure, the sodium potassium ATPase may work in reverse mode leading to increased intracellular sodium and thereby increased intracellular calcium like other ion channels as mentioned above in this heart failure dedifferentiated condition leading depolarized membrane potential. Cardiac glycosides may work in heart failure by inhibiting this reverse mode sodium potassium ATPase. Ouabain has been shown to inhibit lactate i.e. glycolysis can be seen this context (62).

Adrenergic blockade is one of the treatment options in CHF and beta blockers are one of the key drugs used in CHF. Alpha 2 blocker Yohimbine (103) and beta blocker Esmolol (104) has been used to treat cardiac dysfunction in sepsis animal models (11). Alpha 1 blocker Prazosin, beta blocker Propranolol, MAPK inhibitor were used in reducing NO production by blocking the iNOS in cardiomyocytes which was induced by norepinephrine with cytokine has been shown already (40). All these evidences support the hypothesis that Warburg common pathogenesis model may underlie in CHF and sepsis induced cardiac dysfunction. And most of the drugs already tried in CHF can be seen as differentiation therapy.

Hyperglycaemia in sepsis and Diabetes Mellitus (DM) type 1 and 2: Warburg common pathogenesis model may be the underlying mechanism for hyperglycaemia in sepsis, DM 1 and 2. Injury triggering the pathogenesis of these problems are many, for example sepsis may cause hyperglycaemia in septic shock , sepsis or cytokines in DM1, high energy food intake, sedentary lifestyle in DM2. Talchai et al showed dedifferentiation of beta cells may be the cause for DM2 and treatment of diabetes should aim at redifferentition (140).It has been already shown that sympathetic hyper activation may play a role in insulin resistance (134). In all these conditions, 2 key changes occur A) Dedifferentiation of beta cells in pancreas leading to impaired insulin release, either no insulin release or decreased insulin release depends on the level of beta cell dedifferentiation and as seen earlier dedifferentiation of beta cells has been already shown (140-

144) and a recent article showed beta cell dedifferentiation in DM2 in humans (145). B) Dedifferentiation in periphery for example in cardiomyocytes changes the GLUT expression where fetal type GLUT1 are increased and GLUT 4 are decreased leading to insulin resistance and changes in GLUT are already shown in relation to insulin resistance (133,134,149,150).

It has been shown already that DM1 and DM2 may have common underlying mechanism and differ only in the triggering factors and the time it happens (146) and this view point was challenged by many (147). Dedifferentiation of beta cells in the pathogenesis of DM 2 may involve MAPK , NO, PI3K, NFkB (134,140,143,147,148) and insulin resistance in periphery due to dedifferentiation resulting in altered GLUT expression – increased GLUT1 and decreased GLUT4 has been shown already for example in cardiomyocytes and adipocytes (133, 134 ,149, 150). It has been already shown that retinoic acid is necessary for normal beta cell function (151), can be seen in this context which shows maintenance of normal differentiated state of beta cell is necessary for its normal function. Change in GLUT expression with increased GLUT1 and decreased GLUT4 has been shown animal models of sepsis (152,153). Altered GLUT expression in sepsis models may imply the dedifferentiated state of the periphery, and the same dedifferentiated state can be expected to occur in pancreatic beta cells also in sepsis.

Insulin and insulin like growth factors (IGF) activate PI3K/Akt pathway leading to anabolic effects, cell growth and survival. A high level of insulin can hyper activate this pathway leading to Warburg effect and cancer (154). Insulin and thrombin are known to produce VSMC proliferation (155). It is well known that IGF produce proliferation of SMC (156-159).In this context one can see Insulin and IGF may regulate the body as dedifferentiation factors. Hyperglycaemia in sepsis is usually managed by insulin therapy (4). But use of insulin has been shown in some studies to increase the mortality rate in sepsis (4, 160). Using the above evidences, Insulin can be seen as dedifferentiating factor and using it for treating hyperglycaemia may aggravate the already dedifferentiating process which seems to occur in sepsis. Ascorbic acid may be a better treatment option all these 3 conditions – hyperglycaemia in sepsis, DM1 and DM2 will be discussed more in the treatment section.

Renal dysfunction in sepsis, AKI, CKD, PKD and Fanconi's syndrome: Warburg common pathogenesis model may be the underlying mechanism in renal dysfunction in sepsis, AKI and other renal dysfunctions like Fanconi's syndrome. In all these conditions irreversible dedifferentiation of the renal system cells – glomerular endothelial cells, podocytes, mesangial cells, tubular epithelial cells may occur.Most of the related evidence for the hypothesis has been done already in renal dysfunction. Importance of dedifferentiation in renal dysfunction has been already showed by Bonventre and showed it may help in the regenerative process (161). Mesangial cells and Juxtaglomerular (JG) cells even in normal adult state appears to have synthetic / proliferative

properties (162-165). In this context one see the work done by Rinkewich et al on regenerative capacity of renal system and they showed regeneration may occur even in adult life (166). Ozawa et al already showed the importance of glycolysis in relation to podocyte foot process and they also showed dedifferentiated podocytes are highly glycolytic 89% whereas differentiated podocytes are 50 % glycolytic (167).

Based on these evidences, we can see that the renal system is already in a mild Warburg effect state with mild reversible dedifferentiation in at least few renal system cells like podocytes, mesangial cells and JG cells, considering the harsh environment the kidney has to live it seems logical to have this mild Warburg state and this is necessary for normal renal function, for example even the differentiated podocytes have 50% glycolysis shown by Ozawa et al (167) supports this hypothesis. In pathological states of the renal system, it may go to the extreme irreversible dedifferentiation states.Urine lactate has been shown to be increased in Fanconi's syndrome (168). Increased NO due to iNOS activation has been shown in animal model Fanconi's syndrome (169). It has been already shown that in response to injury to renal system, the surviving cells dedifferentiate and repair the injury (161). Renin activity has been already shown to be increased in sepsis (32), this along with many other factors may contribute to the phenotype modulation (165). In poly cystic kidney disease (PKD) the cyst lining cells proliferation can be seen as dedifferentiation (170). Rowe et al showed that glycolysis has been increased in PKD and showed the treatment option by inhibition of glycolysis which decreased the proliferation in PKD (171). Podocytes dedifferentiation leading to glomerular dysfunction and ending in chronic kidney disease (CKD) has been shown already, interestingly retinoids were used as a treatment option to reduce the glomerular dysfunction and it was used as a differentiation therapy in this condition (172). Ascorbic acid as a differentiation therapy may work in renal dysfunctions.

Respiratory dysfunction in sepsis, ARDS and Asthma: Bronchial smooth muscle cells (BSMC) live in highly toxic increased oxygen environment. I speculate that the BSMCs may already in the embryonic dedifferentiated state i.e. mild Warburg dedifferentiation state, to overcome the problems of living in this hostile high oxygen environment, i.e. a mild reversible Warburg dedifferentiation effect is necessary here also in some cells of the respiratory system like renal system as mentioned above. The proliferative properties of Clara cells in terminal and respiratory bronchioles (173) and type 2 alveolar cells (174) in the normal respiratory system can also be seen in this context and this supports the hypothesis that a mild Warburg dedifferentiation effect is necessary for normal respiratory function. As mentioned above in the vascular and cardiac dysfunction section, beta2 ARs are the predominant adrenergic receptors in the primitive foetal dedifferentiated state (66), in this context one can see why catecholamines bronchodialates BSMC. This normal BSMC state is equivalent to the VSMC state in neonatal arteries, and as shown above

norepinephrine paradoxically produced vasorelaxation in neonatal arteries (96), after seeing the Warburg dedifferentiation relation one can see there is no paradox at all in this response. Warburg common pathogenesis model may explain the respiratory dysfunction in sepsis, ARDS/ acute lung injury (ALI) and asthma. BSMC change their cell phenotype to irreversible dedifferentiated – synthetic / proliferative state and change in glycolysis to a high level and the same thing may occur in other cells of the respiratory system. Most of the ground work was already done. Keshari et al in animal model of sepsis to mimic lung injury during sepsis showed regeneration in lungs with type2 alveolar cells and myofibroblasts proliferation, epithelial to mesenchymal transition (EMT) and collagen production (175). Activation of iNOS has been shown in ARDS/ALI (176). Lactic acidosis has been shown already shown in asthma and thought to be due to beta agonist therapy and increased sympathetic activity in asthma (177). Lung lactate is usually not present in normal humans, but lung lactate level has been shown to be increased in Sepsis /ARDS (178, 179). Fibro proliferation in ARDS has already been shown (180). Alveolar cell EMT involvement in pulmonary fibrosis has been shown already (181). Bronchial Smooth muscle proliferation (182-184), and its relation to phenotype change and dedifferentiation, EMT in asthma has been reviewed brilliantly by Bara et al and showed its relation to remodelling process in asthma (76). Methotrexate (MTX), a common antimetabolite anticancer drug inhibited iNOS in cytokine treated lung epithelial cells can be seen in this context (185). Even though not commonly used, MTX is one of the drug options for asthma can be seen in this context.

Coagulopathy: Increased coagulation state and decreased anticoagulation state has been shown in sepsis (186 ,187). Decreased hyaluronan and syndecan which are components of the endothelial glycocalyx were shown to be decreased in sepsis (81) and heparan sulfate levels are elevated in sepsis shows endothelial glycalyx may be degraded in sepsis leading to endothelial dysfunction (80). As discussed earlier(Figure 5), endothelial glycocalyx degradation may trigger phenotype change and decreased in ascorbic acid level plays a crucial role in it. NO has been shown to increase vascular endothelial growth factor (VEGF) and it was related to angiogenesis (25). VEGF has been shown to be increased in sepsis implies angiogenesis may occur in sepsis and these fragile new vessels may cause capillary leak and bleeding complicates the picture further (188). Thrombin has been shown to change the fibroblasts to myofibroblast type (189), we may call this in spirit of Warburg effect as dedifferentiation (Figure 4). As shown earlier, it is well known that thrombin induces VSMC proliferation (155, 190, 191). It has been already shown that heparin is antiproliferative, it inhibited - proliferation of VSMC (192-194), proliferation of uterine SMC (195), mesangial cell proliferation (196).It looks like thrombin may be involved in regulating dedifferentiation state and heparin may be involved in regulating the differentiated state of the vascular system. Overall there is a decrease in anticoagulant state and increase in coagulation state

occurs in sepsis (186,187) and this has to be seen in the context of the cells phenotype state. Heparin has been suggested by many in the treatment of sepsis (197). As said above it may work not only as an anticoagulant but as a differentiating factor. Ascorbic acid has been shown to increase fibrinolytic activity can be seen in this context (198).Many other pathologies also seem to obey the Warburg differentiation dedifferentiation effect but due to space constraint will not be discussed in this review article.

MILD REVERSIBLE WARBURG DIFFERENTIATION DEDIFFERENTIATION EFFECT IS NECESSARY FOR NORMAL FUNCTIONING:

Exercise induced vasodilation in skeletal muscle arteries can be seen in this context. High plasma catecholamine level has been shown during exercise (199) and lactic acidosis (200) during exercise imply glycolysis and this may lead to the embryonic state of the VSMC in skeletal muscle arteries which as shown above may have beta2 ARs as their predominant receptors and catecholamines act on it to produce vasodilation.

Every women in their reproductive period produce a highly regulated tumour called foetus. Even though in pregnancy NO has been shown to be increased in animal models, how this is related to normal pregnancy and complications like preeclampsia is not clear cut (201,202). It is well known that Pregnancy is associated with increased sympathetic activity (203), increased coagulation state and increased insulin level (204) etc., implies pregnancy may be a cancer like condition. Warburg effect has been already related to embryo metabolism (205). A mild and reversible Warburg dedifferentiation effect may be necessary for maintaining normal pregnancy and an exaggerated irreversible Warburg dedifferentiation effect (Figure 1), may cause pregnancy related complications like pre-eclampsia, eclampsia, and gestational diabetes. Due to space constraint, will not be discussed further, but one can relate these conditions to the mechanisms discussed earlier for SHT and Diabetes. It has been already shown that the vascular response was decreased in pregnancy to vasopressors (206), one can see the similarity between this condition and vascular hypo reactivity to vasopressors in septic shock (Figure 3). Also it has been shown in animal model that during pregnancy alpha 1 AR density decreases in aortic VSM (66), can be seen as a change in cell phenotype towards embryonic dedifferentiation state. And this same process when it reaches the irreversible dedifferentiation synthetic / proliferative state may produce the pregnancy complications.

Warburg differentiation dedifferentiation effect in many other normal processes will not be discussed further due to space constraint.

PAULING, GYORGYI , WARBURG AND ASCORBIC ACID : Linus pauling's later half of the life was devoted to ascorbic acid research, who believed ascorbic acid was a universal drug which can be given to many diseases ranging from common cold to cancer. Pauling showed decreased

ascorbic acid level can lead to problems in ECM production and endothelial dysfunction and most importantly its regulation of mitochondrial respiration activation will be lost , all these may lead to Warburg effect and cancer (78). Like Pauling, Gyorgyi who discovered ascorbic acid, devoted his later half of the life in developing the electronic theory of cancer. He believed stopping the electron flux in the mitochondrial electron transport chain could trigger the events leading to Warburg effect and ends in the primitive cancer state that has the better survival advantage and related his electronic theory of cancer with Warburg effect. He believed ascorbic acid is essential for life (207). Irrespective of these giants contribution, interest in ascorbic acid use in diseases and cancer in particular went down. Recently one can see the revival of ascorbic acid and has shown many promising directions ranging from cancer to septic shock (13, 208) and to reach high plasma levels of ascorbic acid it has to be used intravenously(209).

In sepsis ascorbic acid levels were shown to be decreased in sepsis patients and it was used intravenously in a phase 1 trial which showed it is safe and reduces multi organ dysfunction (79).Ascorbic acid has been shown to restore the endothelial dysfunction, insulin sensitivity, restored eNOS, inhibited iNOS (210-212), decreased HIF 1alpha level (213), inhibited TNF alpha induced NfkB (214), enhanced eNOS action by increasing BH4 level (215). Ascorbic acid has shown to inhibit iNOS and restore vascular response to norepinephrine in sepsis animal model (216). Ascorbic acid has been used intravenously which reversed the vascular hyporeactivity to vasopressors during the inflammation made by endotoxin in healthy humans (217). Ascorbic acid has been shown to increase fibrinolytic activity in coronary artery disease patients (198).Also it is well known that ascorbate activate cytochrome C oxidase and is used as a substrate for activating this enzyme(51,78).Ascorbic acid has the potential to be a universal drug which may work in treating many pathologies including all those mentioned in this article ranging from septic shock to cancer. Ascorbic acid works as a differentiating factor regulating the differentiated state of the cell by activating mitochondrial respiration at cytochrome C oxidase there by making the electron flux to proceed normally, also this action includes the removal of mitochondrial respiration inhibition by the uncoupler/respiratory poison, here in septic shock and many pathologies mentioned in the article seems to be due to NO but any uncoupler/respiratory poison can do the same. Also ascorbic acid by decreasing HIF 1 alpha may inhibit the activation of glycolytic enzymes. It helps in maintaining normal endothelial glycocalyx, ECM and endothelial function, this restricts the freedom of the movement of the cells and thus the phenotype change may be prevented. It also works by its commonly known antioxidant function by scavenging the reactive species. In short, ascorbic acid may be a key regulator in maintaining the normal adult differentiated state of the cell and thus maintains order in the human system. Maintaining normal ascorbic acid level in plasma may be essential for normal healthy life. Ascorbic acid can be used to treat most of pathologies as a

differentiation therapy including septic shock. Why a molecule of this importance has not been synthesized in the human body was related to evolution and will not be discussed in this article (78).

TREATMENT OPTIONS FOR SEPTIC SHOCK AS DIFFERENTIATION THERAPY: Treatment should aim at reversing the Warburg effect by activating the mitochondrial respiration either by directly activating the Cytochrome C oxidase or by removing the inhibition of mitochondrial respiration caused by the uncoupler / respiratory poison. Any uncoupler that can do the same job as NO by inhibiting the mitochondrial respiration would trigger the Warburg effect leading to irreversible dedifferentiated states e.g. Cyanide poisoning. When one uncoupler / respiratory poison is causing the disease, the pathology can be treated by **1.** Activating the mitochondrial respiration directly for example by ascorbic acid, caffeine (16), cytochrome C (15) **2.** Removing the uncoupler source for example by reducing the NO in sepsis by using antibiotics, adrenergic blockers, eNOS restoration and iNOS inhibition, **3.** Counterintuitively, one can use the other uncouplers / respiratory poisons that can inhibit the mitochondrial respiration and may work by competitive inhibition thereby activate the mitochondrial respiration, for example this mechanism seems to underlie in the treatment of cyanide poisoning by using sodium nitrite and sodium thiosulfate. As shown above Warburg common pathogenesis model seems to underlie in most pathologies, if most of the diseases have common pathogenesis, then most of the drugs may also work by a common mechanism by reversing the Warburg effect and thus regulates the maintenance of adult differentiated phenotype of the cells by the drugs action on mitochondrial respiration. In that case many safe drugs used in one pathology may be used in some other seemingly unrelated pathologies.

Primary drug options in sepsis:

1. Ascorbic acid should be the primary drug option in septic shock and in many other pathologies and it should be used only by parenteral route and not by oral route. Use of ascorbic acid in sepsis and in many pathologies has been already shown (13, 78, 79).
2. Adrenergic blockers should be used in septic shock as mentioned in the vascular dysfunction section, it has been already used in sepsis and shock states (7,9 - 12, 35, 36, 102). Alpha blockers – may be a better choice in initial state of sepsis and beta blocker may be a better choice in later stages of sepsis, combined alpha + beta blocker may work in all stages of sepsis(Figure 3).
3. Antibiotics
4. Vasopressors should not be given.

The primary drug options along with no vasopressor use - may be sufficient to treat the septic shock.

Secondary drug options:

1. In general, all the antihypertensives may be used for treating septic shock.For example,amlodipine can be used in septic shock and it has been already shown amlodipine inhibited TNF alpha, iNOS expression in VSMC treated with LPS (218).
2. Antiglycolytic drugs – DCA (59),Shikonin (14).
3. Anticancer drugs: ATRA, MTX.
4. Cholinergic agonists or VNS (109,110): Acetylcholine may be helpful, but it also carries the risk of causing bronchoconstriction when given in the initial phase of septic shock. How VNS can be used in septic shock has to be sorted out in future.
5. Andrographolide: Andrographolide has been already shown to restore the normal vascular response in LPS treated rat aorta by inhibiting iNOS and it improved the arterial pressure in septic shock animal model (219).
6. Heparin as mentioned above, will work not only as an anticoagulant but as a regulator of differentiation.
7. Near infrared light (NIR) or Red light: NIR has been shown to activate mitochondrial respiration by its action on cytochrome C oxidase and it has been used in various pathologies (220,221). Red light incubators can be used in future in critical care units.
8. Low dose metformin may help and metformin anticancer role can be seen in this context (222) . Tsoyi et al already shown that metformin improved survival in animal sepsis model by its inhibitory action on high mobility group box1 (HMGB1) (223).
9. Cytochrome C has been already used to activate mitochondrial respiration in sepsis animal model and showed beneficial effects (15).
10. Caffeine (16), like cytochrome C activated mitochondrial respiration in sepsis animal model and produced beneficial effects.
11. Methylene blue (MB): It is well known that MB increase cytochrome c oxidase activity and mitochondrial respiration (224). MB has been used in septic shock patients and showed improved mean arterial pressure but its effect on mortality has not been determined, here MB was used from the viewpoint of soluble Guanylyl cyclase (sGC) inhibition to reduce the NO level (225, 226). Methylene blue should be used only in the late phase of septic shock.
12. Statins (121,122)
13. Sildenafil : Sildenafil has been used in PAH, erectile dysfunction (ED) and it has been shown to restore eNOS ,prevented endothelial dysfunction and decreased iNOS in the ED animal model (227). Sildenafil can be given in later stages of septic shock, whereas in the initial state (Figure 3), where eNOS is already hyper activated, sildenafil may aggravate by further activating eNOS and may complicate the condition.

14. N acetyl cysteine: Can be used to increase glutathione and glutathione may protect the respitatory inhibition by NO (228). But ascorbate itself may rise glutathione level (229).

Due to space constraint i restrict the treatment options. Timing of the drugs plays a key role, as some drugs which were helpful in one phase of the septic shock may not be helpful in other phase e.g. Propranolol may work better only in the late phase of the septic shock.

What not to be used in septic shock treatment: 1. Vasopressors should not be used in septic shock, 2.As discussed earlier because of its effect on proliferation; Insulin carries the risk of double edged sword.

Conclusion:

Warburg common pathogenesis model or Warburg differentiation dedifferentiation effect has the potential to explain not only septic shock but most of the pathologies like SHT, PAH, Atherosclerosis, CHF, ALI/ARDS, Asthma, DM 1 and 2, AKI , PKD, CKD, Fanconi's syndrome etc. This raises the possibility that most of the diseases may have common pathogenesis and most of the drugs may also have a common action, which may be related to the Warburg differentiation - dedifferentiation effect. A mild Warburg differentiation -dedifferentiation effect may be necessary for normal functioning in some specific parts of the body and is necessary for tissue repair. Most of the pathologies tend towards Warburg effect finally. This can be seen as the successful local survival strategy of the cells in response to injuries by returning back to their primitive irreversible dedifferentiated states which may have survival advantage. But this may lead to the disordered state and global failure in organ system/ organism, where order in terms of differentiation is necessary for normal functioning. Death of the organism is due to the immortality pathway chosen by the cells locally. All the processes in the body may have relation to this Warburg differentiation dedifferentiation effect. If the model is experimentally verified, it has the potential to act like a fundamental theorem for medicine. Experimental verification of this model is of paramount importance, as it helps not only in treating septic shock but many other medical problems and will open up new unknown territories.

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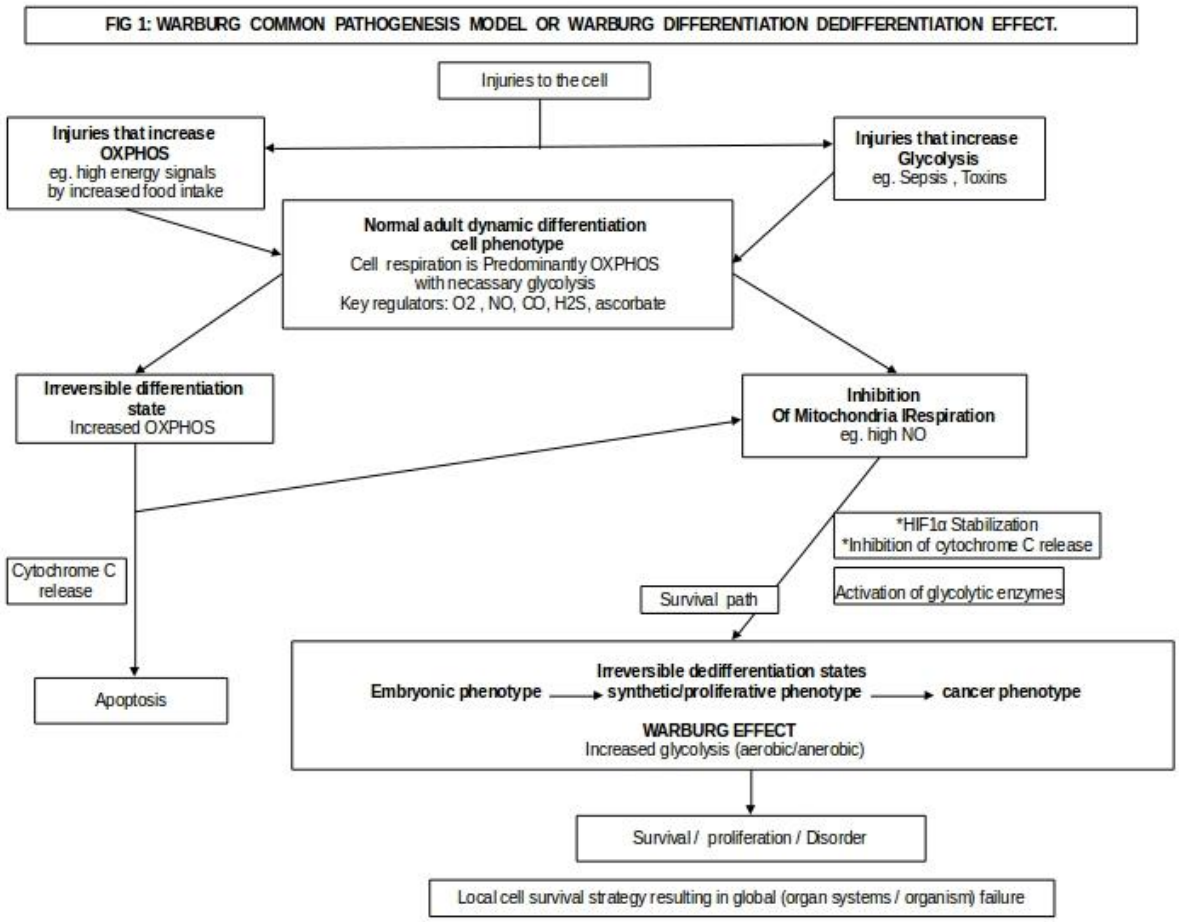

Figure 1: Warburg Common Pathogenesis Model or Warburg Differentiation Dedifferentiation Effect: Injuries to the cells can be of 2 types, injuries that increase glycolysis and injuries that increase oxidative phosphorylation (OXPHOS). Normally the cells will be in adult dynamic differentiation state some of the key factors that regulate this state are oxygen (O2),ascorbate and low levels of nitric oxide (NO),carbon monoxide (CO) and Hydrogen Sulphide (H2S). Injuries that increase glycolysis like sepsis lead to high NO,which irreversibly inhibits the mitochondrial respiration and shifts the cells metabolic phenotype from OXPHOS to glycolytic and this is followed by change in cell phenotype leading to irreversible dedifferentiation states, these shifts may involve hypoxia inducible factor 1α (HIF 1α) stabilization, activation of glycolytic enzymes and inhibition of cytochrome C release. This shift leads to proliferation of the cells and survival, but it also leads to disorder and global collapse of the organ systems / organism which requires order. The other injury which leads to increase in OXPHOS have 2 ways to proceed, one way ends in apoptosis may be due to increased cytochrome C release and the second way leads to survival, which proceeds in same way as discussed for glycolytic injury.

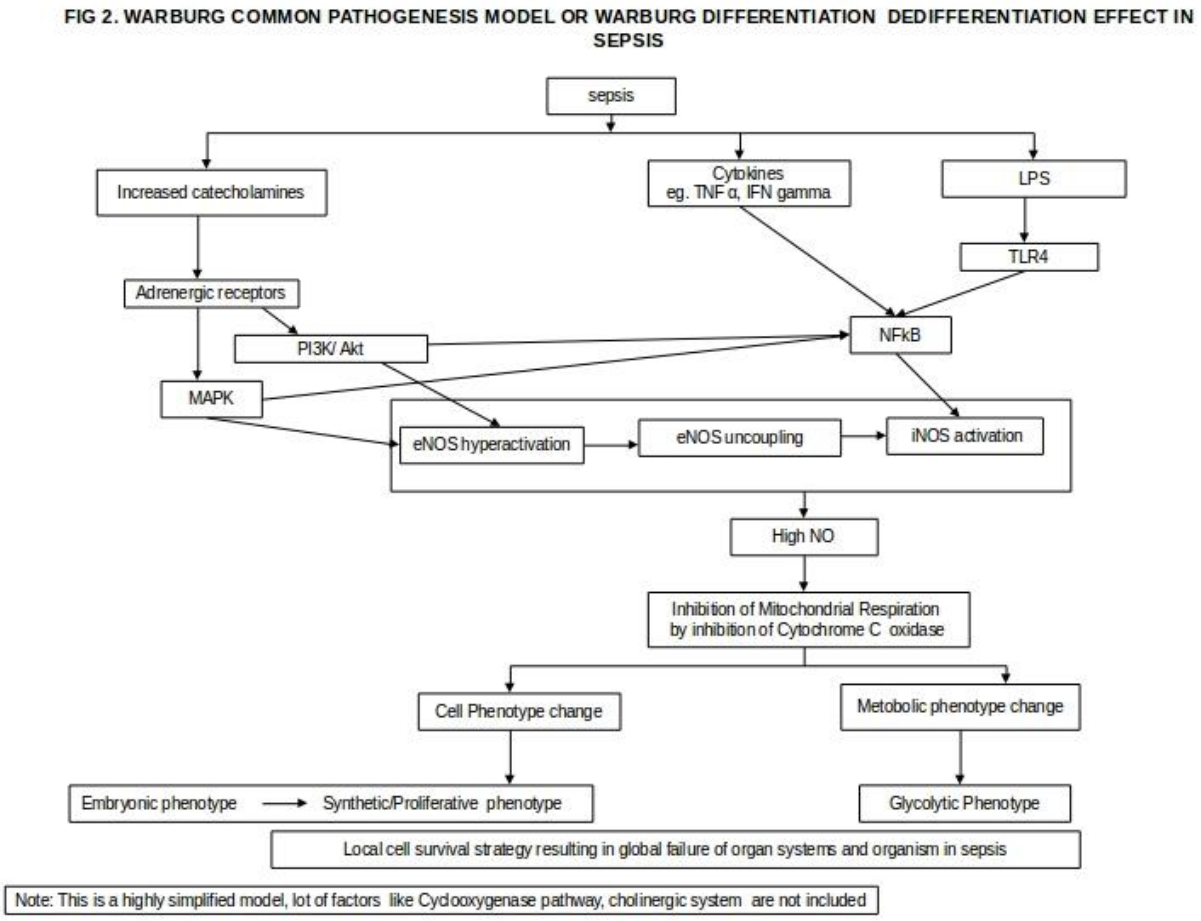

Figure 2 : Warburg Common Pathogenesis Model or Warburg Differentiation Dedifferentiation Effect in Sepsis: In sepsis, increased catecholamines through adrenergic hyper activation, may lead to initial endothelial nitric oxide synthase (eNOS) hyper activation and this leads to eNOS uncoupling and inducible NOS (iNOS) activation. Toxins like lipopolysaccharide (LPS) through toll like receptor (TLR4) and cytokines like tumour necrosis factor alpha (TNFα), interferon (IFN) gamma lead through nuclear factor kappaB (NFkB) to iNOS activation. Mitogen activated protein kinases(MAPK) and phosphatidylinositide 3 Kinase (PI3K) / Akt pathways may be involved. The increased nitric oxide (NO) may irreversibly inhibit the cytochrome C oxidase and thus irreversibly inhibits the mitochondrial respiration, this leads to the metabolic phenotype change from OXPHOS to glycolysis and cell phenotype change from normal adult dynamic differentiated state to irreversible dedifferentiated states – Embryonic phenotype and synthetic / proliferative phenotype. This local cell survival strategy leads to global failure in organ systems and organism.

FIG 3: VASCULAR DYSFUNCTION IN SEPSIS

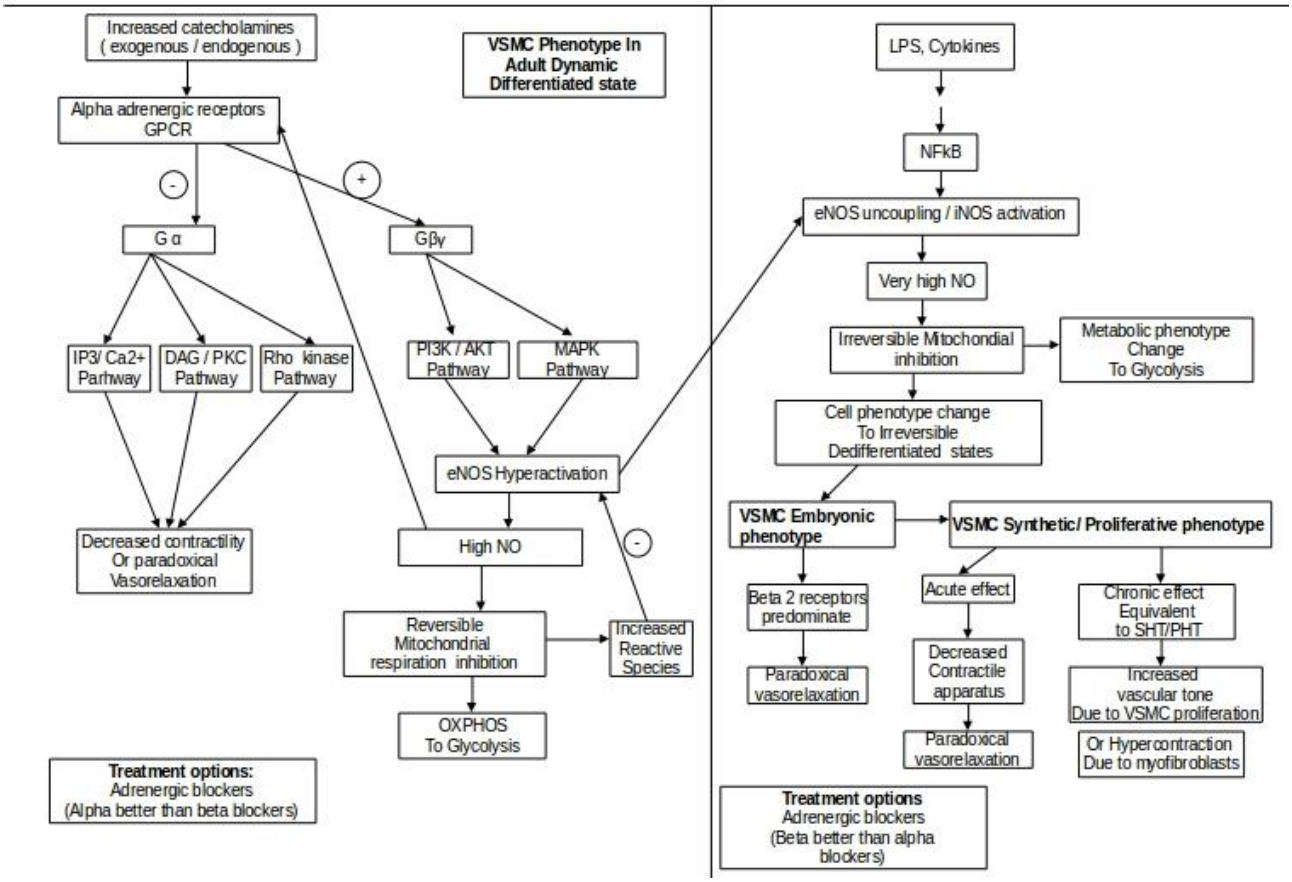

Figure 3: Vascular Dysfunction in Sepsis: Increased catecholamines in sepsis leads to hyperactivation of adreneric receptors(ARs) which are G protein coupled receptors (GPCRs) resulting in activation of G beta gamma subunit (G βγ)pathway, and inhibition of G alpha subunit (Gα) pathway leading to decreased contractility or paradoxical vasorelaxation by inhibition of - IP3/Calcium, DAG /PKC, Rho kinase pathways. Activation of G βγ pathway through mitogen activated protein kinase (MAPK) and phosphatidylinositide 3 Kinase (PI3K) / Akt pathway lead to hyperactivation of eNOS which results in increased NO and reversible inhibition of mitochondrial respiration and reactive speacies production, NO may act on alpha ARs and inhibiting the Gα pathway further. Reactive species may affect eNOS leading to eNOS uncoupling and the same pathways now acivate iNOS. Normally alpha ARs are the predominant ARs in the adult vascular smooth muscle cells (VSMC). Cytokines and lipopolysaccharide (LPS) through NFkB also activate iNOS resulting in high NO production and this irreversibly inhibits mitochondrial respiration at cytochrome C oxidase. This triggers the metabolic phenotype change to glycolysis and cell phenotype change to irreversible dedifferentiation states – initially to VSMC embryonic phenotype and then to VSMC synthetic / proliferative phenotype. Beta ARs may be the predominant ARs in these states resulting in paradoxical vasorelaxation response to catecholamines. For more details please see the text.

FIG 4: PHENOTYPE CHANGE IN VASCULAR SYSTEM DURING SEPTIC SHOCK.

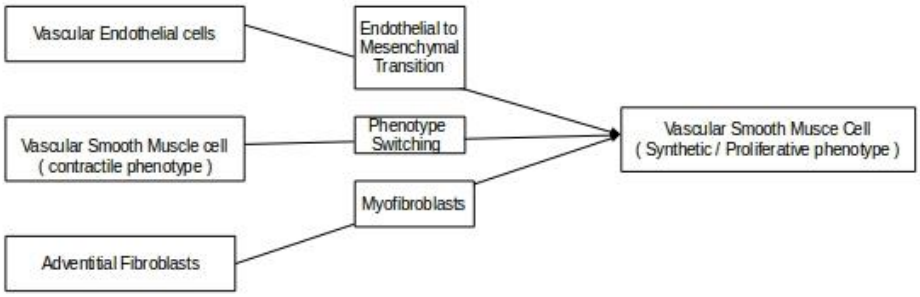

Figure 4: Phenotype change in vascular system during septic shock: In septic shock all the cells in the vascular system – Vascular endothelial cells, Vascular smooth muscle cells VSMC (contractile phenotype), adventitial fibroblasts - tend to move towards Vascular Smooth muscle cell (synthetic / proliferative phenotype). The same phenomena may occur in other organ systems also in the septic shock where different cell types of the specific organ system may tend to move towards one dedifferentiated cell phenotype for that specific system that has the better survival advantage and proliferation.

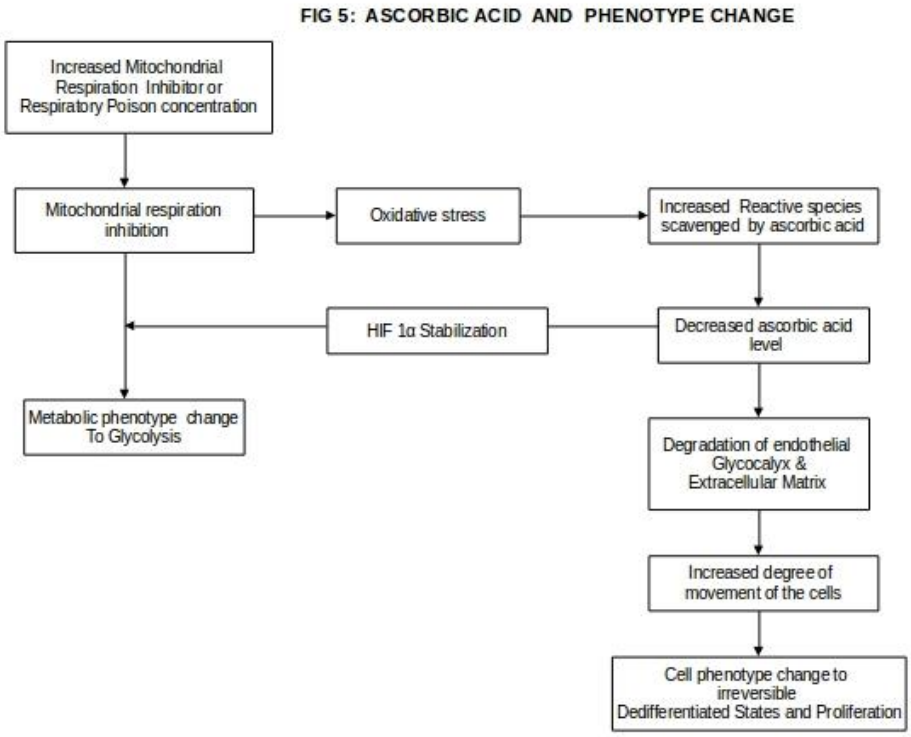

Figure 5: Ascorbic acid and phenotype change: Increased nitric oxide (NO) in sepsis or any respiratory poison in general may inhibit mitochondrial respiration and lead to increased reactive species. Ascorbate level may be decreased due to increased scavenging. Decreased ascorbic acid level may lead to stabilization of hypoxia inducible factor 1 alpha (HIF 1α) and this in turn may activate glycolytic enzymes and lead to glycolysis. Decreased ascorbic acid level may lead to degradation of endothelial glycocalyx and extracellular matrix (ECM). All these changes in endothelium and ECM may lead to increased degrees of movement of the cells, which may trigger the phenotype change to irreversible dedifferentiation states (Warburg effect). Thus normal ascorbic acid level may be essential for the regulation of normal adult dynamic differentiation state of the cells.