Very Low and High Blood Viscosity are Risk Factors for Internal Flow Choking Causing Asymptomatic Cardiovascular Disease

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Very Low and High Blood Viscosity Are Risk Factors for Internal Flow Choking Causing Asymptomatic Cardiovascular Disease

**Short Title:** Low BP ratio and/or high BHCR reduce the risk of Covid-19

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**Keywords:** Acute-Heart Failure, Asymptomatic hemorrhage, Biofluid choking, Covid-19, BHCR, Sanal flow choking.
Abstract

Background
It is well known that the common aftereffect of administration with the blood-thinning-drug for lowering the blood-viscosity is bleeding. And very often during the blood-thinning medication, without any preceding symptoms, asymptomatic-hemorrhage (AH) and the acute-heart-failure (AHF) are testified. Of late (2021) researchers reported (PMID: 34326352) that symptoms are intensifying on asymptomatic cardiovascular-diseases and the various types of neurological-disorders linked with COVID-19 pandemic due to the nanoscale Sanal-flow-choking.

Objectives
Our aim was to establish the proof of the concept of the Sanal flow choking in cardiovascular system (CVS) causing AH and AHF by correlating multitude of parameters, viz., the blood pressure ratio (BPR), biofluid/blood-heat-capacity-ratio (BHCR), blood viscosity, blood density, stenosis (in terms of the vessel cross-sectional area and/or the hydraulic diameter of the vessel) and ejection fraction in terms of fluid flow rate. In this regard an infallible closed-form analytical model was aimed to develop. We also aimed for correlating multitude of variables for setting unchoked flow conditions in CVS for negating AH and AHF. We were scheduled in vitro and in silico studies for corroborating the proof of the concept of flow choking in CVS.

Methods
The proof of the concept of Sanal-flow-choking and unchoked flow conditions in CVS are established using the closed-form-analytical-methodology by setting with the multitude of variables. Speciation analyses of blood samples of healthy subjects (human being/Guinea pig) are carried out for the BHCR estimation of blood samples of healthy subjects (human being/Guinea pig) by invoking in vitro method. Asymptomatic pressure-overshoot due to the
Sanal flow choking and transient shock wave generation in a simulated artery (a case with gas embolism) with a divergence region is demonstrated using *in silico* method.

**Results**

We established the proof of the concept of internal flow choking in CVS causing cardiovascular risk through the closed-form analytical, *in vitro* and *in silico* methods. We discovered that at a critical blood-pressure-ratio (BPR), the internal-flow-choking occurs anywhere in the CVS with the sudden expansion/ divergence/ bifurcation / stenosis / occlusion or vasospasm regions without prejudice to the *percutaneous coronary intervention* (PCI).

Mathematical models disclose that the reasonably high and low blood viscosity are risk factors of asymptomatic cardiovascular disease. *In vitro* results reveal that nitrogen (N$_2$), oxygen (O$_2$), and carbon dioxide (CO$_2$) are the leading gases evolved from fresh-blood samples of the healthy subjects (human-being and Guinea-pig) at a temperature range of 37-40$^\circ$C (98.6-104$^\circ$F). It increases the risk of flow-choking leading to asymptomatic cardiovascular-diseases and the various types of neurological-disorders. This physical situation is more critical for the COVID-19 patients as it leads to AH and AHF. We observed through *in vitro* studies that the healthy Guinea-pig is having thermal-tolerance level higher than the human being in terms of BHCR. The possible episode of Sanal flow choking and shock wave generation in an artery with the divergent/ bifurcation region is demonstrated through *in silico* methods.

**Conclusions**

An overdose of blood-thinning drug for decreasing the viscosity will enhance the *Reynolds number*, which creates high turbulence level causing an augmented boundary layer blockage factor leading to an early undesirable biofluid/Sanal flow choking. It enhances the possibilities of cavitation and the *Sanal-flow-choking* heading to the shock wave generation followed by
transient pressure-overshoot causing memory effect (stroke history) in viscoelastic vessels.

Determining the exact blood-thinning dose is critical for achieving the preferred therapeutic efficacy and annulling undesirable flow-choking causing asymptomatic-hemorrhage (AH) and the acute-heart-failure (AHF). We could establish herein that the lopsided blood-thinning administration enhances the risk of the Sanal-flow-choking due to the augmented boundary layer blockage (BLB) factor. We concluded that cardiovascular risk could be reduced by simultaneously lessening the blood-viscosity and flow turbulence by increasing thermal-tolerance-level in terms of BHCR and/or by decreasing the blood pressure (BP) ratio.

Condensed Abstract

Herein, we established the proof of the concept of internal flow choking in CVS causing cardiovascular risk through the closed-form analytical, in vitro and in silico methods. An over dose of blood-thinning drug will enhance the Reynolds number, which creates high turbulence level causing an augmented boundary layer blockage factor leading to an early undesirable biofluid/Sanal flow choking at a critical blood-pressure-ratio (BPR). The fact is that in nanoscale vessels when the pressure of fluid increases, average-mean-free-path decreases and thus, the Knudsen number reduces. It leads to the physical situation of no-slip boundary condition with compressible-viscous flow effect. Sanal-flow-choking is a compressible-viscous flow effect establishing a physical condition of the sonic-fluid-throat, at a critical blood pressure ratio (BPR). We concluded that asymptomatic-hemorrhage (AH) and acute-heart-failure (AHF) are transient-events as a result of internal flow-choking in nanoscale and/or large vessels followed by the shock wave creation and transient pressure-overshoot. We concluded that cardiovascular risk could be reduced by simultaneously lessening the blood-viscosity and flow turbulence by
increasing thermal-tolerance-level in terms of BHCR and/or by decreasing the blood pressure (BP) ratio.

**Introduction**

The theoretical discovery of the nanoscale *Sanal-flow-choking* [1] is a paradigm shift in risk assessment for hemorrhagic stroke and other neurological disorders. This study is the continuation of our previous work published in Nature *Scientific Reports* [1]. Of late (2021) researchers reported that data are increasing on the various asymptomatic cardiovascular diseases associated with COVID-19 pandemic [1-3] due to the Sanal flow choking [1, 4-6] (PMC7267099). Through our companion papers we have reported that Sanal flow choking leads to asymptomatic aneurysm [6], hemorrhagic-stroke [7], acute myocardial infarction [8] and other neurological-disorders [4-14] on Earth and Human spaceflight if the vessel geometry is having divergence, bifurcation, stenosis and/or occlusion regions. In this paper we are correlating multitudes of variables causing internal flow choking leading to AH and AHF. There are two types of internal flow choking (see Fig. 1(a-c)), viz., (i) biofluid/blood flow choking due to plaque or stenosis or occlusion (i.e., geometry effect of vessels), (ii) Sanal flow choking due to boundary layer blockage (i.e., fluid dynamics effect) [11].

The acute-heart-failure (AHF) is known as the fatal disease worldwide over the centuries. Very often, the fatal AHF occurs without prior indications of coronary artery obstruction (angina). According to the WHO [15], the *Ischemic heart disease* (IHD) [16] and *asymptomatic hemorrhage (AH) / stroke* are the world’s biggest killers. M.Packer [17] categorically reported that the acute-heart-failure (AHF) is a transient event and not a disease and put forward a coherent claim for multidisciplinary research for drugs-discovery [18]. V.R.S.Kumar et al. [1, 4-14] reported in a series of connected papers that such transient events instigating the
(a) Nanoscale flow choking in an artery with the plaque.

(b) Biofluid/blood flow choking in an artery with plaque and bifurcation.

(c) Sanal flow choking in an artery with bifurcation and without plaque.

Figure 1(a-c) The demonstration of internal flow choking in arteries.
Internal Flow Choking: The Central Illustration

(a)

(b)

(c)

(d)

(e)

(f)
Figure 2(a-o). The demonstration of various physical situations of Internal flow choking (Biofluid/Sanal flow choking) in the cardiovascular system without prejudice to Percutaneous Coronary Intervention (PCI).
cardiovascular diseases are due to an internal flow choking (biofluid and/or Sanal flow choking – see Fig.1(a-c) and Fig.2(a-o)). It is followed by shock wave generation and pressure-overshoot in the cardiovascular system (CVS), which happens at a critical systolic-to-diastolic blood-pressure-ratio (BPR).

Internal flow choking could occur without prejudice to the Percutaneous Coronary Intervention (PCI). The real scientific truth is that, at a critical BPR, the internal flow choking followed by shock wave generation occurs anywhere in the CVS with sudden expansion/divergence, vasospasm, bifurcation, stenosis and/or occlusion regions (see Fig.2(a-o) – the central illustration). The critical fact is that, the internal biofluid/blood flow choking is uniquely regulated by the heat-capacity-ratio (HCR) of the fluid (blood / biofluid / gas). It has been established that the Sanal flow choking phenomenon occurs, in the real world flows (continuum and non-continuum) due to the compressible viscous flow effect, in the form of a sonic-fluid-throat effect as a result of BLB factor [1, 4-14]. Note that altered variations of blood viscosity and turbulence lead to flow choking in CVS. It leads to cavitation, shock wave generation and transient pressure-spike. Internal flow choking (biofluid / Sanal flow choking) could happen in all vessels including vasa vasorum and nanoscale tubes [1]. The fact is that in nanoscale vessels when the pressure of fluid increases, average-mean-free-path decreases and thus, the Knudsen number reduces. It leads to the physical situation of no-slip boundary condition with compressible-viscous flow effect [1]. Sanal-flow-choking is a compressible-viscous flow effect establishing a physical condition of the sonic-fluid-throat, at a critical blood pressure ratio (BPR = SBP/DBP) due to the BLB factor. The concepts of Sanal flow choking [1,4-6] is well connected herein with the prevailing concepts in the biological sciences for
discovering possible methods for negating the risk of biofluid/Sanal flow choking heading to asymptomatic cardiovascular diseases.

**Analytical Methodology**

Using the compressible flow theory, the following closed-form analytical models (see Eqs.1-5) have been developed for correlating the BHCR, BPR, biofluid/blood-kinematic-viscosity, biofluid/blood-density, diastolic-blood-pressure (DBP), hydraulic-diameter of the vessel, the vessel cross-sectional area, blood/biofluid velocity, Reynolds number \((Re)\), boundary-layer-blockage (BLB) and ejection-fraction in terms of biofluid/blood flow rate (BFR) for predicting the risk of flow-choking in cardiovascular system (CVS) causing asymptomatic-hemorrhage (AH) and the acute-heart-failure (AHF).

Equations 1 & 2 are two independent and complementing conditions for maintaining the unchoked flow condition in the CVS. Note that flow gets choked when the flow Mach number \((M)\) reaches one. Therefore, it is mandatory to retain the flow Mach number always less than one for prohibiting the internal flow choking in CVS, which is reflected in Eq.2, Eq.2a and Eq.2b with the multitude of variables. Note that Eq.2a and Eq.2b are the corollary of Eq.2, which explain the role of the vessel blockage, in terms of the vessel cross-sectional area and the ejection fraction in terms of biofluid/blood flow rate (BFR), on the risk of flow choking leading to AH and AHF.

\[
\text{BPR} = \frac{SBP}{DBP} < \left( \frac{\text{BHCR} + 1}{2} \right)^{\frac{\text{BHCR}}{\text{BHCR} - 1}} \quad (1)
\]
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\( \frac{M}{1} \) \hspace{1cm} (2)

\( \frac{\text{Reynold number}(\text{kinematic viscosity of blood/biofluid})}{\text{Hydraulic diameter of the vessel}} \left[ \frac{\text{Blood density}}{(\text{BHCR})/\text{(DBP)}} \right]^{-1/2} < 1 \) \hspace{1cm} (2a)

\[ \left[ \frac{\text{(Blood / biofluid flow rate)}_{\text{local}}}{(\text{ BHCR})_{\text{lowest}}} \right] \left( \frac{\text{blood/biofluid viscosity} \_\text{local}}{(DBP)(\text{Vessel cross – sectional area})_{\text{local}}} \right)^{-1/2} < 1 \] \hspace{1cm} (2b)

\[ LCHI = \left( \frac{(\text{BHCR})_{\text{lowest}} + 1}{2} \right)^{\frac{1}{\text{BHCR}_{\text{lowest}}}} \] \hspace{1cm} (3)

\[ UCHI = \left( \frac{(\text{BHCR})_{\text{blood}} + 1}{2} \right)^{\frac{1}{(\text{BHCR})_{\text{blood}}}} \] \hspace{1cm} (4)

Note that for prohibiting the internal flow choking in CVS all subjects must maintain BPR lower than the lower-critical-hemorrhage-index (LCHI), which could be estimated from the lowest value of the BHCR of evolved gases in the CVS (see Eq.3). For instance, if carbon dioxide is the dominant gas in the CVS it is mandatory to maintain BPR lower than 1.8257 for creating an unchoked flow condition for prohibiting the shock wave generation and transient pressure-overshoot causing the AH and AHF. The LCHI can be estimated through in vitro study aiming for finding the dominant gases evolved from blood samples of each subject (human being or animal) at different thermal levels. The upper critical hemorrhage index (UCHI) can be predicted (see Eq.4) from the specific heat of blood at constant pressure (\( C_p \)) and the specific heat of blood at constant volume (\( C_v \)), estimated using the Differential Scanning Calorimeter - Perkin Elmer DSC 8000.
The boundary-layer-blockage (BLB) in the blood vessels can be predisposed by the variations in the biofluid viscosity and the BHCR of the flowing gas / nano plasma. Equation 5 relates the artery diameter ($d_i$), the inflow Mach number ($M_{inlet}$), the axial Mach number ($M_{axial}$), and the BHCR, which is derived from compressible flow theory [4-6].

$$BLB = 1 - \left[ \frac{M_{inlet}}{M_{axis}} \right]^{1/2} \left[ \frac{1 + \left( \frac{BHCR - 1}{2} \right) M_{axis}^2}{1 + \left( \frac{BHCR - 1}{2} \right) M_{inlet}^2} \right] \frac{BHCR + 1}{4(BHCR - 1)} d_i \quad (5)$$

The earlier researchers, all together, presumed that the human blood is an incompressible fluid (i.e., $C_p = C_v$). Such an assumption is obviously not true as the human blood specific volume (or density) does change with temperature or pressure. Note that all fluids in nature are compressible [6-11] and therefore $C_p$ is always greater than $C_v$ [6]. It establishes that the Sanal flow choking and shock wave generation occurs at UCHI in CVS having divergent or bifurcation regions without any plaque. At the Sanal flow choking condition, the creeping flow (low subsonic flow) will get augmented in a uniform cross-sectional area duct due to the area blockage caused by the boundary-layer-displacement-thickness (i.e., BLB in Eq.5). The total 3D boundary layer blockage (TBLB) at Sanal-flow-choking condition ($M_{axis} = 1$) for diabatic flows is obtained as (see Eq.5a) [5-7],

$$TBLB_{@\text{sonic \ fluid \ - throat}} = \left[ 1 - \frac{M_{inlet}}{M_{axis}} \right]^{1/2} \left[ \frac{2}{(BHCR)_{lowest} + 1} \left( 1 + \left( \frac{(BHCR)_{lowest} - 1}{2} \right) M_{inlet}^2 \right) \right]^{(BHCR)_{lowest} + 1} d_i \quad (5a)$$
(a) An idealized physical model of an artery with divergent region

(b) SANAL Chart: Condition for prohibiting AH and AHF

Fig. 3(a-b) Demonstrating the condition for prohibiting the Sanal-flow-choking with respect to the percentage blockage factor in a 3D vessel with divergent region [8].
The BLB factor in the blood vessels could alter due to the seasonal effects (see Fig. 3(a)) as a result of the variations in the biofluid/blood viscosity [4-14, 19-24]. If the blood vessel geometry is similar to the convergent-divergent (CD) nozzle shape (due to various physical situations as seen in Fig. 1(a-c) & Fig. 2(a-o)), the divergent region of the CD duct creates supersonic flow immediately after the internal flow choking (biofluid / Sanal flow choking). It leads to shock wave generation and transient pressure-spike [1, 4-14] as the case may be. Note that a minor disturbance to the supersonic flow creates shock waves in the downstream regions. Therefore, bulging or tearing of the vessel will always be at the downstream region of the sonic point (see Fig. 2(a-o)). This physical situation could be forecast through reliable multi-phase, multi-species in silico models [5-14] verified and validated at the Sanal flow choking condition. Further discussion on in silico model is beyond the scope of this paper. Figure 3(a) shows the idealized physical model of an artery with the divergent region and Fig. 3(b) shows the corresponding SANAL chart (the solution of Eq. 5a) relating to a case of gas embolism with carbon dioxide as the chief evolved gas. Figure 3(b) explicitly reveals that irrespective of the percentage blockage of the artery, the critical BPR determines the risk of the biofluid/Sanal flow choking leading to asymptomatic cardiovascular diseases. The SANAL chart also confirms that a reduction in the blockage factor decreases the flow Mach number for satisfying the conservation law of nature (i.e., continuity condition set by nature), which reduces the risk of internal flow choking. It is crystal clear from the closed-form analytical model that for negating the internal flow choking all subjects must retain BPR always lesser than the LCHI. Analytical model presented herein verifies that the stents could reduce the risk of the heart attack (i.e., due to the reduction in the flow Mach number) but it is not better than drug owing to the fact that the biofluid/Sanal flow choking could happen with and without stent (see Fig. 2(d-f)) at a critical
BPR. The self-explanatory equations (see Eqs. 1-5), derived from the compressible flow theory [5,6], are highlighting various influencing parameters for prohibiting the biofluid/Sanal flow choking in the artery. Note that the ejection fraction is reflected in Eq.2b in terms of biofluid/blood flow rate (BFR). It is apparent from the closed-form-analytical model (see Eq.2b) that the ejection fraction is not the lone factor for declaring the risk of AHF. It is coupled with the local cross-sectional area of the vessel, local biofluid/blood velocity, local Reynolds number, BHCR_{lowest} and the local static pressure (i.e., diastolic blood pressure (DBP)). The local Reynolds number $(Re=\frac{\rho v D_H}{\mu})$ can be estimated from the local hydraulic diameter of the vessel $(D_H)$, the mean velocity of the biofluid/blood fluid $(v)$, the density of the biofluid/blood $(\rho)$, and the dynamic viscosity of the biofluid/blood $(\mu)$. The Reynolds number $(Re)$ helps predict flow patterns in different fluid flow situations. At low Reynolds number, flow tends to be dominated by laminar (sheet-like) flow, while at high Reynolds number, flow tends to be turbulent. The high turbulence level increases the boundary layer displacement thickness (i.e., the boundary layer blockage factor) causing an early Sanal flow choking.

In high risk subjects (BPR close to LCHI and/or Mach number close one) a slight oscillation in the BPR predisposes to the transient choking and the unchoking events heading to arrhythmia. It is appropriate to mention here that, generally heart valve problems involve aortic and mitral valves. It is possibly because of its geometric shape similar to CD nozzle flow passage. Further deliberations of valve problems, aneurysm and arrhythmia is beyond the scope of this article. Note that the biofluid/Sanal flow choking could create unusual transient pressure-overshoot in vessels with divergent/bifurcation regions [4-14], which increases memory effects (stroke history) leading to artery tear in the subsequent stroke. The magnitude of the pressure-
overshoot depends on the strength of the shock. It is decided by the flow Mach number and the
heat capacity ratio of the fluid.

**In vitro Methodology**

We have estimated the heat capacity ratio (HCR) of blood, obtained from the healthy human
being and one male *Guinea pig* living in the southern part of the Indian union, using the
*Differential Scanning Calorimeter (DSC) - Perkin Elmer DSC 8000. Blood samples of healthy
subjects are obtained from an approved blood bank in India, viz., Bangalore Blood Bank &
Diagnostic Laboratory (A Unit of Indian Trust For Social Action, License Number:
KTK/28C/1/94). Samples are collected from healthy subjects after the informed consent. And
blood sample of healthy Guinea pig is directly obtained from the animal living in the
Government of India approved Animal House Facility associated with the Faculty of Pharmacy
M.S.Ramaiah University of Applied Science, Bangalore - 560054, INDIA (Registration number:
220/PO/ReBi/2000/CPCSEA). Please note that none of the Authors handled the animal for
withdrawing blood from a four-week old healthy male *Guinea pig*. The guinea pig blood sample
was drawn by an authorized person and provided to us by the officials of Animal House Facility
upon our request. All the experimental methods reported herein are in accordance with relevant
guidelines and regulations. Please note that the ethical committee approval is not required by
the national legislation of Indian union for conducting the blood sample test of healthy human
being and animals reported herein, which are applicable to all the authors and their affiliated
institutions in India. We confirm that all experimental protocols were approved by the National
Centre for Combustion Research and Development (NCCRD) of the Indian Institute of Science
(IISc) for the blood sample tests of healthy human being and animals. Also note that for
randomized studies the blood bank who supplied blood samples of healthy subjects obtained the
written and informed consent from all the healthy human beings prior to the test conducted at NCCRD/IISc, India. The in vitro methodology is available at https://osf.io/p7kmg [10].

The Guinness Book of World Records (2014) reveals that a person with a reported heatstroke having a body temperature of 115 °F (46.1 °C) is the highest-reported body temperature, who survived after medical care. Therefore, in this pilot work we have carried out detailed in vitro studies beyond the highest-reported body temperature for different research objectives. **Table-1 and Table-2** show the measured BPR, BHCR (estimated using in vitro method) and UCHI (analytically predicted using Eq.4) of healthy subjects of age 23-56.

Table-1 Prediction of the UCHI from the heat capacity ratio of fresh blood samples of healthy human beings of age 23-56.

| Batch No. | Blood Group | SBP/DBP | BPR | BHCR | UCHI @ 37.5°C |
|-----------|-------------|---------|-----|------|---------------|
| 3073      | O+          | 150/90  | 1.666 | 3.5  | 3.11          |
| 3074      | A+          | 120/70  | 1.714 | 2.76 | 2.691         |
| 3078      | B-          | 150/90  | 1.666 | 2.7292 | 2.709       |
| 3080      | O+          | 150/90  | 1.666 | 2.9935 | 2.824       |
| 3082      | A+          | 140/96  | 1.458 | 2.6759 | 2.64         |

**Table 2. Upper Critical Hemorrhage Index (UCHI) of Healthy Subjects [10]**

| Specimen Reference | SBP/DBP mm Hg | BPR  | Heat Capacity Ratio (HCR) of Healthy Subjects | Upper Critical Hemorrhage Index (UCHI) |
|--------------------|---------------|------|-----------------------------------------------|--------------------------------------|
|                    |               |      | 37.5°C | 40°C | 37.5°C | 40°C | 37.5°C | 40°C | 37.5°C | 40°C | 37.5°C | 40°C |
| HM35A+             | 110/76        | 1.44 | 5.69   | 5.37 | 4.33   | 4.15 |
| HM23A+             | 130/60        | 2.16 | 118.29  | 20.42 | 61.75  | 12.10 |
| HM48B+             | 110/80        | 1.37 | 7.44   | 7.03 | 5.28   | 5.06 |
| HM37O+             | 120/60        | 2    | 18.07  | 6.39 | 10.88  | 4.71 |
Fig. 4(a-c) The mass spectrum of N$_2$, O$_2$, and CO$_2$ evolved as a function of both time and temperature obtained from blood samples of healthy subjects.

Figure 4(a-c) shows the mass spectrum of N$_2$, O$_2$, and CO$_2$ evolved as a function of both time and temperature obtained from blood sample tests of healthy subjects (human being and Guinea pig). The mass spectrometer used in the present study is Perkin Elmer SQ8T, which uses the Electron Impact detector. During our comprehensive in vitro studies, we have noticed that the gases evolved from the fresh blood sample depends on the blood temperature, the heating rate, blood group, age and the blood pressure value. It is evident from Fig.4(c) that CO$_2$ is the dominant gas for human being whereas nitrogen gas is dominant (Fig.4(a)) in the blood sample of Guinea pig.

The estimated LCHI of all healthy human being is found 1.82, which is based on the evolved dominant carbon dioxide gas (BHCR = 1.289). In the case of Guinea pig, the LCHI is estimated as 1.89, which is based on the dominant nitrogen gas (BHCR = 1.4). We found that there are variations in the heat capacity of blood samples collected in three different Vacutainers of same healthy subjects. The anticoagulant reduces the BHCR and susceptible to an early biofluid choking in blood vessels, including vasa vasorum, causing high cardiovascular risk. The most popular consequence of medication with anticoagulant drug is bleeding. The clinical reports of
various investigators [2, 3, 24, 27-30, 43] are corroborating the authenticity of our analytical models and in vitro data reported herein.

It is crystal clear from Fig.4 that the possibilities of the Sanal flow choking in the animal (Guinea pig) is lower than in the human being at the same temperature level as the heat capacity ratio (HCR) of the main gas generated in the animal is found constantly higher than the human being. The mass spectrum of N$_2$ is observed greater in Guinea pig whereas in the healthy human being CO$_2$ is observed greater. The HCR of N$_2$ is 1.4 and that of CO$_2$ is 1.289. It corroborates that at the same thermal loading condition, the artery of Guinea pig gets choked only at a BPR of 1.8929 and the artery of the healthy human being gets an early choking at a BPR of 1.8257. Therefore, we concluded that the thermal tolerance level of the healthy Guinea pig is higher and the cardiovascular risk is lower than the human being under identical conditions. Therefore, increasing the thermal tolerance level of the human being is important for reducing the risk of AHF due to the Covid-19 or otherwise. More specifically, if BHCR is relatively high the evaporation temperature of blood will also become high and as a result the risk of gas embolism followed by internal flow choking can be reduced.

In Silico Methodology

In an effort to demonstrate the proof of the concept of BLB factor persuaded Sanal flow choking we have carried out in silico studies with low-subsonic inflow (i.e., creeping flow) conditions (a case with gas embolism) using a validated flow solver [9]. We have demonstrated the pressure overshoot at the downstream region of the simulated artery with a divergent region (see Fig.5) causing asymptomatic hemorrhage and/or acute heart attack as the case may be. The preliminary single phase in silico results (see Fig.5) show the Sanal flow choking and the shock-wave generation at the creeping flow heading to the transient pressure-overshoots.
(stroke) in the downstream region of an artery with divergent port. It substantiates that the transient episode of biofluid/Sanal-flow-choking is a paradigm shift in the diagnostic sciences of acute-heart failure.

Fig. 5 In silico results show the Sanal-flow-choking and shock-wave generation at the subsonic inflow condition (creeping flow) leading to the transient pressure overshoots (causing memory effect / stroke) in the downstream region of an artery (where tissue death (infarction) occurs) with divergent port as a result of the CD nozzle flow effect (a case with gas embolism) [7, 8].

It is evident from Fig. 5 that when static pressure decreases (i.e., DBP in biological systems) the chances of attaining the Sanal flow choking condition is very high. Note that flow choking is uniquely is regulated by BHCR. Therefore, total-to-static pressure ratio (i.e., systolic-to-diastolic blood pressure ratio (BPR)) and BHCR are important determinants in biological systems for identifying the asymptomatic cardiovascular risk. The diminishing shock waves followed by the transient pressure-overshoots create memory effects in multiple locations of the
artery during the entire lifespan of all subjects having oscillating BPR creating choking and unchoking physical situations.

**Statistical analysis**

All *in vitro* studies were carried out independently at least six times for repeatability and also for establishing that the data generated are in agreement with the true value in each independent experiment. *In silico* studies are carried out after the code validation.

**Outcomes**

*In vitro* study proved that the specific heat of blood at constant pressure (C$_p$) is always higher than the specific heat at constant volume (C$_v$). Therefore, the validity of the analytical models (Eqs.1-4) derived from the compressible flow theory for predicting the risk of flow choking leading to AH and AHF presented herein is established. During the *Hyphenated techniques* at the atmospheric pressure we have detected N$_2$, O$_2$, CO$_2$, Ar and one undefined composite gas (m/z = 28.5) in blood samples of healthy subjects at various intensity at the temperature range of 37-40$^\circ$C (98.6-104$^\circ$F) and above [10]. We observed that the gasification temperature of healthy *Guinea pig* blood is higher than the healthy human being. The BHCR of healthy subjects taken from the EDTA and Lithium Heparin tubes was found significantly lower (31-32 %) than the fresh blood samples of the same healthy subjects tested within 5 minutes of collection. We observed that CO$_2$, the gas with the lowest HCR is relatively and consistently higher in the healthy males than the healthy male *Guinea pig* of four weeks old (see Fig.4). Note that HCR of CO$_2$ is 1.289, therefore a subject with gas embolism, with CO$_2$ as the dominant gas, the biofluid choking occurs (see Eq.1) at a BPR of 1.8257, which is the lower critical hemorrhage index (LCHI). It reveals that patients who are taking blood-thinning medication must maintain their BPR always less than 1.8257, as dictated by Eq.1, for reducing the risk of internal flow...
choking leading to *asymptomatic vascular diseases* [27, 28]. This condition is particularly important for subjects with relatively low BHCR.

The closed-form analytical model, *in vitro* and *in silico* study results reported herein reveal that for a healthy-life all human being/animals with the high BPR inevitably have high BHCR for reducing the risk of AHF by prohibiting biofluid/Sanal-flow-choking heading to shock wave generation and transient pressure-spike causing memory effect (stroke history). The preliminary single phase *in silico* results (see Fig.5) show the phenomenon of Sanal-flow-choking and shock wave generation at the subsonic inflow condition (creeping flow) leading to the transient pressure-overshoots (stroke) in the downstream zone of an artery with a divergent port.

**Results**

We discovered that at a critical blood-pressure-ratio (BPR), the internal-flow-choking occurs anywhere in the cardiovascular system (CVS) with the sudden expansion/divergence/bifurcation / stenosis / occlusion or vasospasm regions. The critical fact is that; the internal-flow-choking is uniquely regulated by BHCR. Analytical findings reveal that the relatively high and low blood viscosity are cardiovascular risk factors. Equation 2a discloses the conflicting requirements for achieving the unchoked flow condition for reducing the risk of AH and AHF.

The fact is that while using over dose of blood thinners, blood viscosity reduces and *Reynolds number* increases and flow becomes turbulent. It creates an early flow choking due to the development of the higher boundary layer blockage factor. Note that the turbulent boundary layer displacement thickness is higher than laminar boundary layer thickness. Herein we established that the disproportionate blood-thinning treatment increases the risk of *internal flow choking* due to the enhanced boundary-layer-displacement-thickness (boundary layer blockage
(BLB) factor) due to an increase in flow turbulence in the CVS due to an increase in Reynolds number \( (Re) \) as a consequence of relatively low blood viscosity \( (BV) \).

**Discussion**

Through closed-form analytical models (see Eqs.1-4) we could correlate the BHCR, BPR, blood viscosity, port geometry of the vessel and ejection fraction, along with other parameters contributing for internal flow choking. The infallible closed-form analytical models with the multitude variables shed light on finding solutions for decreasing the risk of AH and AHF due to biofluid choking and/or Sanal flow choking. Note that internal flow choking leads to shock wave generation in CVS (see Fig.2(a-o)). Please note that the internal flow choking (biofluid choking and/or Sanal flow choking) is a physical situation created by nature at a critical-pressure-ratio (cpr) (please see the supplementary materials Movie S1, S2, & S3). In biological systems, the CPR is the ratio of systolic-to-diastolic blood pressure \( (BPR = SBP/DBP) \). It is uniquely controlled by biofluid/blood-heat-capacity-ratio \( (BHCR) \). It is a well-known scientific fact that the internal flow choking leads to supersonic flow development if the downstream region of the vessel geometry is having divergence and/or bifurcation regions. It is important to note that a minor disturbance to the supersonic flow leads to shock wave generation and transient pressure-overshoot and memory effects (stroke history) causing asymptomatic cardiovascular episodes. This is corroborated with the observation of Packer [17]. More specifically, shock wave is inherently a transient phenomenon, which create transient pressure-overshoot causing acute-heart-failure (AHF). It is important to note that multitudes of variables highlighted on the causes and effects of AH and AHF, over the decades, are supported with our findings [1, 4-14]. Briefly, herein, we could establish, based on the infallible closed-form analytical models supported with *in vitro* and *in silico* results, that AH and AHF are transient-events due to flow choking and shock wave
generation. Please note that the exact solution obtained from the closed-form analytical model is not required any verification using in vitro data. Nevertheless, in vitro data generated from the blood sample test of healthy subjects provided herein for corroborating our theoretical discovery. In vitro data is also used for establishing the unchoked flow condition in healthy subjects having relatively high BPR (> 1.8257) and BHCR (see Table-2). The occurrence of choked flow condition and shock wave generation causing hemorrhagic-stroke is demonstrated using the clinical data of a Covid-19 patient [1]. Briefly, there is no need of large data base for establishing the choking and unchoking conditions in cardiovascular system. More specifically, the accurate measurement of BPR and the high fidelity in vitro estimation of BHCR of all subjects are sufficient for the risk assessment of asymptomatic cardiovascular diseases due to the phenomenon of internal flow choking.

We have discovered through closed-form analytical models that if we increase the thermal tolerance level in terms of blood heat capacity ratio (BHCR) and/or decrease BPR, we can control concurrently blood viscosity and turbulence and prohibit undesirable flow choking (see Eq.1-4). This is a remarkable finding reported herein. At the threshold of the internal-flow-choking condition, a minor oscillation in BPR for both hyper and hypo subjects is likely to aggravate the risk of the asymptomatic cardiovascular disease. Our finding is corroborated with the clinical report presented by Razavi et al. [43] (PMID: 32322398; PMCID: PMC7163302; DOI: 10.1016/j.nmni.2020.100669) from Mazandaran University of Medical Science, Iran. Note that if BHCR is relatively low (i.e., low thermal tolerance) blood will get vaporize early in Covid-19 patients and others leading to gas embolism. At this condition if BPR is increasing the chances of asymptomatic cardiovascular diseases will be high due to the undesirable internal flow choking. Therefore, increasing the thermal tolerance level in terms of
BHCR and/or decreasing the BPR is a possible remedy for negating the internal flow choking causing AH and AHF. We discovered through analytical methodology that BHCR is a unique parameter, which can control concurrently blood viscosity and turbulence. Briefly, high BHCR reduces blood viscosity and turbulence.

Generally, we consider blood flow is laminar in the CVS. The fact is that blood flow becomes turbulent while taking blood thinning drugs. It is well known that the blood thinning medication reduces the whole blood viscosity (BV) and as a result Reynolds number (Re) increases and the laminar blood flow becomes turbulent. This physical situation results in the shortfall of energy in the form of friction. It, obviously, increases the boundary layer blockage (BLB) in the blood vessels. It generates heat and augment the internal energy causing a decrease in BHCR, which is corroborated with in vitro results. Furthermore, turbulence augments the perfusion pressure crucial to drive the blood flow.

The shear rate or shear rate history of the blood/biofluid can alter viscosity. Blood viscosity could vary due to seasonal effects too [19-40]. Note that temperature of blood reduces during the winter season causing a rise in viscosity of blood. During the summer season the inverse effects happen [9]. All these lead to corroborate that the boundary layer blockage (BLB) factor initiating the Sanal flow choking [4-7] could vary due to the variations in blood viscosity (BV) as a result of the seasonal effects and/or due to the usage of the blood-thinning drugs [9]. Truly, BLB persuaded flow choking (biofluid/Sanal flow choking) is more susceptible in the winter season than the summer season because the viscosity of blood will be relatively high at a low temperature. Therefore, the risk of flow choking would be high during the winter season than
in the summer season. It leads to AH and AHF. These findings are corroborating with the available literature data [6-14, 24].

Equation 1 reveals that the critical ratio of BPR for flow choking is an exclusive function of BHCR. It is crystal clear from Eq.2a that stenosis could increase the risk of flow choking. Note that in Eq.2a, stenosis is taken in terms of the hydraulic diameter of the blood vessel. Eq.2a also tells us that stent fix for raising the hydraulic diameter of the vessel could reduce the risk of flow choking. Closed-form analytical models presented herein reveal that stent implant is certainly not a stable solution for lessening the risk of AHF, without having suitable control on the other multitude parameters highlighted in the models (see Eqs.1, 2, 2a & 2b).

Though all the prevailing percentage demarcations of the ejection fraction (EF) are significant for the diagnosis, until the theoretical discovery of Sanal flow choking [1, 4-14] these outcomes were not aided by any closed-form analytical model for taking any reliable conclusion. Therefore, we have reported herein the infallible closed-form analytical models for establishing the internal flow choking with the multitude of variables (see Eqs.1-4). Equation 2b explains the desirable biofluid/blood flow rate (BFR) or ejection fraction for predicting the risk of AHF. Equations 2a-b are showing the correlation of the ejection fraction in terms of local BFR and the flow turbulence level in terms of Reynolds number of normal heart along with the other governing factors viz., vessel geometry, thermodynamic and fluid dynamics properties of blood/biofluid. These factors contribute for flow choking and unchoking in CVS at various seasons. It is evident from Eqs.2a-b that the risk factor changes on the coupled effects of the ejection fraction, the local vessel cross-sectional area (VCA), BHCR, DBP and local blood viscosity. Mathematical models presented herein reveal that, at a constant VCA and DBP a reduction in BHCR and a rise in Reynolds number together or separately, increases the
likelihoods of internal flow choking. Seemingly (see Eq.2a) a rise in kinematic viscosity increases the risks of flow choking. On the contrary, a rise in kinematic viscosity decreases the risks of flow choking by reducing the Reynolds number. This infallible analytical finding reveals that there is a safe range of blood viscosity for negating the flow choking of each and every subject. Note that flow choking depends up on the joint effects of the other governing factors (see Eqs.1, 2, 2a & 2b). Therefore, in the absence of BHCR data (still unknown to medical science), the dose of blood-thinning drugs must be recommended subjected to the condition set in Eqs.2a & 2b based on the clinical data (multitude of variables highlighted in Eq.1-5) of individual subject.

Note that using over-dose of drug to decrease the blood viscosity only makes the turbulence worse and escalates the possibilities of cavitation and flow choking because as stated earlier turbulent flow creates higher BLB factor than laminar flow. The BLB in the blood vessel generates heat and augment the internal energy causing a decrease in BHCR, which is vulnerable to an early flow choking in the cardiovascular system (CVS). On these rationale, we established herein that the uneven blood-thinning medications increase the possibilities of internal flow choking causing AHF, which is supporting with the established laboratory index, International normalized ratio (INA). Briefly, an overdose of blood-thinning drug enhances the Reynolds number causing to the large turbulence level in the vessel and as a result the laminar flow could be intruded and converts to turbulent flow causing an early internal flow choking (biofluid and/or Sanal flow choking). Flow choking causes a transient sharp pressure-spike as a result of the occurrence of shock waves, at the creeping inflow condition without any iota of symptoms of the plaque, in an artery with sudden expansion / divergence / bifurcation / vasospasm (see Fig.2(a-o) as the Central Illustration). Admittedly, internal flow choking can develop in
nanoscale vessels [1] and also in the coronary artery with and without stent (Percutaneous Coronary Intervention). When the pressure of the nanoscale fluid increases, the average mean free path decreases and thus, the Knudsen number reduces leading to a no-slip boundary condition with compressible viscous (CV) flow effect [1]. The Sanal-flow-choking is a CV flow effect. It is established as the flow choking caused by the BLB factor at the creeping inflow condition at a critical pressure ratio. Briefly, the discovery of internal flow choking in CVS is a scientific breakthrough and a paradigm shift in the diagnostic science of asymptomatic vascular diseases. Internal flow choking (biofluid/Sanal flow choking) leads to the shock-wave generation followed by pressure overshoot causing tearing of the blood vessels. The tearing depends on the memory effects (stroke history) and the thermo-viscoelastic properties of the vessel. This fundamental research paper, started from the chemical rocket science [1,6,9], aims to discover the basic cause(s) of bleeding during the administration of blood-thinning drugs. It also aims to recommend possible conditions for reducing the risk of internal flow choking causing AH and AHF.

Note that large swings in BPR create periodic choking and unchoking phenomena causing atrial fibrillation (AFib) or an irregular heartbeat (arrhythmia) in both hyper and hypo subjects. In light of the Covid-19 pandemic, the thermal tolerance level of blood needs to be examined in terms of variations in the BHCR for the risk assessment of the ischaemic heart disease. The European Society of Cardiology (ESC) reported (2020) that subjects with cardiovascular risk (CVR) factors and proven cardiovascular disease (CVD) denote an open population when suffering from the Covid-19. ESC also added that subjects with cardiac injury in the assessment of Covid-19 have a greater risk of illness and demise (www.escardio.org). This article sheds light for discovering new avenues in biological science for devising new blood-thinning drugs
for increasing BHCR and/or decreasing BPR. Note that companion drugs along with the traditional blood thinners for reducing the risk of flow choking causing AH and AHF [1, 6-14, 42] is also envisaged. We concluded that the cardiovascular treatment should be targeted based on blood pressure ratio (BPR), instead of blood pressure levels alone, along with the BHCR optimization, in chronic heart failure patients [40].

The intermittent internal flow choking, due to large fluctuations in BPR, leading to transient pressure-overshoots created throughout the life-span in the CVS create the vessel walls more stiff due to memory effects (stroke history). Such intermittent flow choking in any viscoelastic vessels having stenosis/divergence/bifurcation regions are prone to rupture, possibly the downstream region from sonic point, in the subsequent choking and the shock wave development. Briefly, we have reported conclusively herein (see Eq.1) that high BPR and low BHCR are risk factors for the flow choking causing transient episodes in CVS. An elevated systolic BP (SBP) and lower diastolic BP (DBP) reflects arterial aging [41]. It happens due to the repeated Sanal-flow-choking and “shock wave generation” causing memory effects ending with so-called natural mortality due to the life-threatening-vessel tearing due to gradual stiffness. The physical situation of Sanal-flow-choking is more dangerous in Covid-19 patients, which could lead to stroke epidemic. In high risk subjects, (i.e., BPR is very close to the LCHI), a slight oscillation in the BPR predisposes to the choking and the unchoking phenomena, which could lead to arrhythmia and memory effect. Briefly, this study sheds light for exploring new avenues in biological science for discovering the actual cause of “natural mortality” through autopsy for devising new drugs for increasing the healthy lifespan of all subjects in the universe (on earth, human space station and other planets). Discovering a companion medicine with the
traditional blood-thinning drugs for reducing the risk of internal flow choking causing asymptomatic cardiovascular diseases is also envisaged herein.

Conclusions

An over dose of blood-thinning drug will enhance the *Reynolds number*, which creates high turbulence level causing an augmented boundary layer blockage factor leading to an early undesirable biofluid/Sanal flow choking. We concluded through infallible closed-form analytical models that relatively **high blood viscosity** and relatively **low blood viscosity** are risk factors for the early flow choking. It leads to asymptomatic-hemorrhage (AH) and the acute-heart-failure (AHF). These findings are correlating with the established index INA. Therefore, the actual effect of viscosity on flow choking needs to be established for taking preventive strategies for negating the risk of AH and AHF. On this rationale, it is desirable, rather necessary, perhaps inevitable to affirm a condition for preventing the undesirable flow choking in the CVS, which we have presented herein in terms of blood viscosity, density, *Reynolds number*, BHCR, BPR, DBP and stenosis (vessel geometry). We concluded that a single drug capable to enhance the BHCR and suppress the turbulence level and/or a companion drug along with the conventional blood-thinning drug is inevitable for meeting the conflicting requirements (*i.e.*, *decrease viscosity and turbulence simultaneously*) for prohibiting the flow choking of all the subjects for reducing the risk of *asymptomatic vascular diseases*. In high risk subjects (*BPR close to the LCHI*) a minor fluctuation in the blood pressure ratio (BPR) influences to the choking and the unchoking phenomena, which could lead to *arrhythmia*. In a nutshell, we have ascertained decisively that low BP ratio and the high-BHCR reduce the risk of flow choking as dictated by Eq.1, which is an indisputable physical condition, without any *ex vivo* or *in vivo* model support, for prohibiting *asymptomatic stroke* in any vessel [34-37]. We concluded that
for a healthy-life all subjects with high-BP ratio (BPR) inevitably have high-BHCR for reducing the risk of internal flow choking (biofluid/Sanal-flow-choking) triggering the AH and AHF due to the shock wave generation and transient pressure overshoot [1, 6-14, 44, 45]. Note that magnitude of the pressure-overshoot depends on the strength of the shock wave (normal/oblique shock wave) [46]. We corroborated herein that, the acute-heart-failure (AHF) is a transient episode [17] due to the internal flow choking followed by shock wave generation and transient pressure-overshoot.

Study limitations

Conducting *in vivo* studies in all subjects require ethical clearance.

Translational Outlook

Large randomized blood sample tests for BHCR estimation along with BPR measurement, adequately in all seasons in all blood groups, across the globe are needed for discovering new drugs capable to increase the BHCR and/or decrease the BPR in all seasons for reducing the risk of *internal flow choking* in all subjects.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Code availability statement

The mathematical algorithm used for generating analytical results are available with the author VS. The code used for generating *in vitro* results are available with the authors RSB and CO.
The code used for generating the \textit{in silico} results is available with the authors NC and AS. The raw data required to reproduce the results are available with the corresponding author and could be shared upon reasonable request.

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Author Contributions

VRSK: Conceptualization, analytical modeling, manuscript drafting; SKC: In vitro conceptualization, manuscript editing; PKR: In vitro conceptualization, manuscript editing; RSB: In vitro and data generation; NC: In vitro, in silico and project support, VS: Modeling and simulation support, AS: In silico simulation support, CO: Resources
Supplementary Files

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- APPENDIX30August2021.pdf
- MovieS1DemonstratingBoundarylayerblockageinducedSanalFlowChokingInsilicoreresult.avi
- MovieS2FlowchokingandShockwavegenerationinaViscoelasticTubewithVasospasmlInvitroresult.mp4
- MovieS3flowchokingwithairasfluid.mp4