Intertraffic of Endothelin 1 and Thrombospondin 1 between lungs and myocard via pulmonary circulation can alter cardiac loads, tissue integrity and atrial blood coagulability [version 1; referees: 1 approved]

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Abstract

Similar expression patterns of mRNA profiles for Endothelin 1 (ET-1) and Thrombospondin 1 (TSP1) from GeneAtlas U133A, gcrma, suggest that these two mediators are dominantly synthesized in the myocard and lungs. This paper proposes that intertraffic of these two mediators between myocard and lungs via pulmonary and coronary vessels optimizes cardiopulmonary functions and maintains their tissue integrity. A controlled delivery of endocrine mediators to the left and to the right heart is done by the coronary sinus (CS) that drains venous blood to the right atrium, and Thebesian veins (TVs) that open in all four heart cavities.

Myocard and pulmonary capillaries are connected as a bidirectional portal system. Mediators from lungs can directly influence myocardial cells after entering the coronary circulation, while mediators in the myocardial venous blood that drain into the right heart will initially affect lungs. Strain induced myocardial ET-1 secretion into the right heart and pulmonary circulation increases the right heart afterload by constricting pulmonary vasculature. The same action reduces the left heart preload. Pulmonary ET-1 secretion can protect lungs from overperfusion by increasing the left heart afterload through constriction of peripheral arterioles. Chronic tissue overexposure to ET-1 leads to pulmonary and myocardial fibrosis.

TSP1 availability is important in tissues under mechanical stress, since TSP1 is an adhesive glycoprotein involved in cell-to-cell and cell-to-matrix interactions. Pulmonary and myocardial TSP1 secretion that enter the fibrillating left atrium can mimic actions of the platelet-derived TSP1 in promoting the thrombus formation.
Introduction
Unexpectedly similar expression patterns of mRNA profiles for Endothelin 1 (ET-1) (http://biogps.org/#goto=genereport&id=1906) and Thrombospondin 1 (TSP1) (http://biogps.org/#goto=genereport&id=7057) in GeneAtlas U133A (at http://biogps.org), suggest that these two mediators are dominantly synthesized in myocard and lungs.

ET-1 is known as one of the strongest vasoconstrictors, while TSP1 is one of the key inhibitors of angiogenesis that is also important in the maintenance of tissue integrity and remodeling. A direct link between these two mediators and cardiopulmonary circulation seems to exist, since it has been reported that loss-of-function thrombospondin-1 mutations were found in familial pulmonary hypertension², a clinical condition treatable with bosentan, an ET-1 receptor blocker³. An attractive possibility is that TSP1 and ET-1 might act as a pair of opposing mediators in the regulation of resistance in pulmonary vessels.

This paper proposes that endocrine intertraffic of these two mediators between myocard and lungs via pulmonary and coronary vessels might be important in optimizing cardiopulmonary function and maintaining tissue integrity of both organs.

Part I: Lungs and myocard as a self-regulated unit dependent on bidirectional portal-type endocrine loops
An important issue is whether mediators synthesized in the myocard can be selectively diverted between the pulmonary circuit and the systemic circuit. Here the proposed idea is that a controlled delivery to the left and to the right heart is done by the peculiar myocardial venous circulation that includes coronary sinus (CS) that drains venous blood to the right atrium, and Thebesian veins (TVs) that open in all four heart cavities⁴,⁵, particularly numerous at the ventricle apex and at papillary muscles base⁶.

It was observed that the blood flow through TVs depends on the heart muscle stretching. In inactive heart muscle perfused through coronaries under pressure, more fluid can escape through TVs than through CS⁷, suggesting that fluid drainage via Thebesian veins in comparison to other veins might be more important in situations when heart chambers are stretched, due to the volume load.

If we look at the cardiopulmonary circulation in more detail (Figure 1), the pulmonary capillaries are in the serial position to the myocardial capillaries, meaning that mediators from lungs

Figure 1. Schematic drawing of cardiopulmonary circulation. The pulmonary capillaries are in the serial position to the myocard, so mediators from lungs can directly influence myocardial cells, after entering the coronary circulation. Myocardial venous blood that drain into the right heart (mainly via coronary sinus (CS) and also via the right heart Thebesian veins (TVs)) initially affects lungs before being diluted in the systemic circulation.
can directly influence myocardial cells after entering the coronary circulation. Myocardial veins to the right heart (mainly CS and also the right heart TVs) place myocardial capillaries in the serial position, in front of the pulmonary capillaries. Any mediator in the myocardial venous blood drained in the right heart will initially affect lungs before being diluted in the systemic circulation.

This unique setting can be described as a double portal system in which myocard and pulmonary capillaries are bidirectionally connected via short endocrine loops. Other, better-known examples of portal circulations in our body are unidirectional, since the tissue of the secondary capillaries (adenohypophysis or liver) has no way of endocrine action directed selectively on the primary organ (hypothalamus in the former and stomach and intestines in the latter). Instead of that mediators from secondary capillaries return to the heart and enter pulmonary circulation.

It should be noted that although this paper is focused on ET-1 and TSP1, due to their high synthesis rates in lungs and myocard, various other substances can act through these short, portal-type loops that connect cardiopulmonary organs.

Both lungs and myocard are rich in various receptors, so local perfusion clearance is expected for many mediators in the blood that passes through lungs and myocard.

As shown in Table 1, any surplus of myocardial mediators can leave the heart muscle through the left heart Thebesian veins and enter the systemic circulation, or leak to the right heart through CS and the right heart TVs. In the latter case, the right heart veins act as a shortcut from myocard to pulmonary circulation.

On the other hand, substances synthesized in lungs enter the left heart and aorta. Some of these can directly affect the myocard via coronary arteries, and their surplus can return to the lungs via CS and the right heart TVs.

An important consequence of the described setting is that for any disorder caused by direct cardiopulmonary endocrine loops it can be expected to remain undetectable by measuring the peripheral vein blood levels of involved mediators. This means that new diagnostic methods are probably required to recognize patients with problems caused by an alteration in cardiopulmonary control loops.

### Table 1. Proposed expected settings of myocardial ET-1 secretion during rest and exercise (LV - left ventricle; RV - right ventricle).

<table>
<thead>
<tr>
<th>Proposed control loops mediated by ET-1 secreted from the myocard</th>
<th>Resting/light activity</th>
<th>Heavy exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output</td>
<td>&lt;10 L/min</td>
<td>&gt;12 L/min</td>
</tr>
<tr>
<td>Activation of the Frank-Starling mechanism</td>
<td>LOW</td>
<td>MAXIMAL</td>
</tr>
<tr>
<td>Increased heart rate</td>
<td>NO</td>
<td>YES due to increased demands by skeletal muscles</td>
</tr>
<tr>
<td>ET-1 secretion from the myocard</td>
<td>low to moderate</td>
<td>high due to muscle stretching and action of other mediators</td>
</tr>
<tr>
<td>Myocard venous blood output during the heart cycle to the LA via coronary sinus (peak flow during late systole and early diastole)</td>
<td>continuous except during the atrial systole (P-Q interval)</td>
<td>increased</td>
</tr>
<tr>
<td>Thebesian veins</td>
<td>atrial TVs</td>
<td>diastolic (T-Q interval), depends on ventricular stretching and atrial systoles</td>
</tr>
<tr>
<td>Ventricular wall TVs (peak blood flow during the late diastole)</td>
<td>highly increased due to the stretching of TVs orifices, atrial systoles and increased heart rate</td>
<td></td>
</tr>
<tr>
<td>Constriction of pulmonary arteries due to ET-1 from CS and TVs from the right side</td>
<td>RV output</td>
<td>decreased</td>
</tr>
<tr>
<td>RV output</td>
<td>moderate exposure to ET-1 help in more uniform perfusion of pulmonary tissues</td>
<td></td>
</tr>
<tr>
<td>RV afterload</td>
<td>increased</td>
<td></td>
</tr>
<tr>
<td>LV preload</td>
<td>decreased</td>
<td></td>
</tr>
<tr>
<td>Constriction of systemic arteries due to TVs from the left side</td>
<td>LV output</td>
<td>decreased</td>
</tr>
<tr>
<td>LV output</td>
<td>low exposure of systemic arteries to ET-1</td>
<td></td>
</tr>
<tr>
<td>LV afterload</td>
<td>increased</td>
<td></td>
</tr>
<tr>
<td>RV preload</td>
<td>decreased</td>
<td></td>
</tr>
<tr>
<td>RV preload</td>
<td>Protective effect of ET-1 secreted in both arterial circuits comes from limiting heart work by increasing afterload and decreasing preload of both ventricles</td>
<td></td>
</tr>
</tbody>
</table>
of 343.5 and 307.5. The mean EDN1 value for all reported tissue samples is only 13.28, clearly suggesting that cardiac myocytes and lungs synthesize much more ET-1 than all other tested tissues and cells.

A separate issue is the identification of target tissues for the circulating ET-1. Data of endothelin A receptor (gene EDNRA) (http://biogps.org/#goto=genereport&id=1909) were extracted from the probeset 216235. High EDNRA mRNA levels were reported in uterus, cardiac myocytes, heart, prostate, lungs, liver, appendix and skeletal muscle. In the second probeset 204463, uterus, prostate and lungs have the highest EDNRA values, while in the probeset 204464, fetal lungs and uterus standout as tissues with the highest EDNRA mRNA values.

A plausible interpretation is that lungs and cardiac myocytes produce so much ET-1 that the surplus of ET-1 molecules leaks into the circulation. Other tissues are able to synthesize ET-1 in modest quantities, probably acting as a paracrine mediator. This interpretation is in concordance with papers that report cardiac secretion of ET-1 in animal models.

Table 1 is based on the expectation that the myocardial ET-1 synthesis increases due to stretching and increased work of the cardiac muscle, during heavy exercise as well as in pathologic conditions that dilate heart chambers. Exposure to humoral and paracrine mediators also influences the ET-1 synthesis. So, although atrial TVs can remain open during almost the whole heart cycle, with the exception of the short atrial systole (visible as the P-R interval on ECG), the ventricular TVs probably drain more blood during late diastole, when ventricles are stretched to maximal length and under low pressure. During ventricular systole TVs openings are reduced in size, the intraventricular pressure is higher than in the heart veins, particularly in the left ventricle, so most of the myocardial venous blood probably leaves through the coronary sinus.

When considering the mRNA distributions for ET-1 and its receptor A together, here the proposed interpretation is that lungs and cardiac myocytes produce so much ET-1 that the surplus of ET-1 molecules leaks into the circulation. Other tissues are able to synthesize ET-1 in modest quantities, probably acting as a paracrine mediator. This interpretation is in concordance with papers that report cardiac secretion of ET-1 in animal models.

- It is similar for the myocardial ET-1 secreted in the left heart via thebesian veins. This secretion also increases the left heart afterload by constricting peripheral arteries and the consequence is the reduction of the right heart preload due to the reduced venous return.

These simple changes in resistance of pulmonary and systemic arteries help the myocard to adapt to many different settings of physical work, particularly to quickly alleviate extremely low afterload and thus reduce the increased venous return (the right heart preload) during intense muscular work.

Part III: Local TSP1 synthesis in tissues under continuous mechanical stress

It is known that blood levels of thrombospondin 1 can be altered in patients with ischemic disease, malignancy, particularly in pancreatic cancer patients or metabolic problems. Based on many TSP1 roles, some synthesis is expected to be almost ubiquitous, but only few cells/tissues require so much thrombospondin 1 that the local surplus normally leaks into circulation.

There are two important aspects of the reported TSP1 mRNA values (http://biogps.org/#goto=genereport&id=7057). The first is that almost all tested cells/tissues contained this mRNA, and the second is that few cells/organisms have shown high levels. Among the main sources of TSP1 synthesis are Cardiac Myocytes, Bronchial Epithelial Cells, Smooth Muscle Cells and Uterus. All these cells/tissues are unique by their special ability to actively or passively adapt to changes in the cellular shape and surface area. Cardiac myocytes and smooth muscle cells form tissue layers that contract by reducing their area in a manner of bidimensional shrinkage:

- During smooth muscle contractions in arterial vessels, digestive organs or uterus, axially undefined smooth muscle cells are not constrained. They change their shape by bidimensional shrinking of the covered area.
- During myocardial contractions, many small interconnected cells form a meshwork. Although individual myocard cells can contract only along their axial skeleton, the myocard layers bidimensionally shrink, due to the linear shortening of cellular units that form meshwork layers.
- In lung tissue, there is no active contraction during inspiration and expiration, since the physical work of breathing is done by skeletal muscles that change the thoracic volume. Lungs expand passively according to the intrathoracic pressure and available space. These passive changes of alveolar volume force alveolar cells to adapt in their shape and covering area.

In all these three examples, changes in the cell shape are repetitive. This means that the tissue structure integrity strongly depends on interconnections between cells. This is a point where plentiful TSP1 availability becomes important, since TSP1 is an adhesive glycoprotein that mediates cell-to-cell and cell-to-matrix interactions, binds to fibrinogen, fibronectin, laminin, type V collagen and integrins. This means that beside other factors...
(glucose, insulin), the local synthesis of TSP1 is probably related to the average mechanical stress, in tubular structures governed by the Law of Laplace.

Part IV: Health disorders possibly related to the alteration of ET-1 and TSP1 cardiopulmonary loops

Based on the mentioned link of ET-1 and TSP1 to pulmonary fibrosis, it can be assumed that other health issues can be linked to the imbalance in pulmonary or myocardial synthesis of these two mediators.

Disorders possibly related to the ET-1 over-exposure of myocard and lung tissue

Table 2. shows possible damage of supraphysiologic myocardial and pulmonary ET-1 secretion. Two auto-endocrine loops that start and end in the same tissue are proposed. The first possibility is that the presence of endothelin A receptors on cardiac myocytes can explain the ET-1 mediated heart hypertrophy. Beside pulmonary ET-1, the left heart Thbesian veins can increase deliverance of ET-1 to the coronary circulation and lead to heart hypertrophy and to the diastolic dysfunction.

The second autocrine loop is possible in patients with a significant left-to-right cardiac shunt. Surplus of pulmonary ET-1, due to increased pulmonary perfusion can leak through the shunt opening from the left heart to the right side. Once on the right side, the excess ET-1 leaves the right ventricle and through pulmonary arteries reach lungs. This recycling of pulmonary ET-1 via left-to-right shunt can lead to pulmonary hypertension and fibrosis. Both conditions are components of the Eisenmenger’s syndrome, often treated by bosentan, a blocker of endothelin receptors.

Possible risk of thrombus formation due to local accumulation of TSP1 in the left atrium

Some patients with long-lasting atrial fibrillation never suffer from peripheral embolism, despite not being on anticoagulant therapy, while others experience peripheral artery embolisms despite regular therapy. Only rare patients develop thrombi in the right atrium, although both atria are fibrillating, with similar magnitude reductions in ejection velocities. These observations point to the unsolved question why is the left atrium so much more prone to the thrombus formation during fibrillation.

It is here assumed that the local rate of TSP1 synthesis probably depends on the local myocardial and pulmonary pathology, some patients produce a surplus of myocardial TSP1 due to cardiac dilatation, myocytes stretching or metabolic conditions, while diverse pulmonary problems can augment leaking of pulmonary TSP1 into circulation.

As shown in Table 3, the right atrium receives the systemic venous blood, normally poor in TSP1. On the other hand, the coronary venous blood via CS and TVs, normally contain some myocardial TSP1, but endocrine factors or local condition within the heart muscle can increase the TSP1 content. The situation is similar in the right ventricle.

<table>
<thead>
<tr>
<th>Three proposed endocrine loops that control vascular resistance in target tissues</th>
<th>Physiological ET-1 secretion</th>
<th>Supraphysiological ET-1 exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET-1 from the myocard</td>
<td>Endocrine loop through pulmonary circulation</td>
<td>Left heart muscle &gt; coronary sinus and TVs that open in right side &gt; pulmonary arteries &gt; arterioles &gt; lungs</td>
</tr>
<tr>
<td></td>
<td>Endocrine loop through systemic circulation</td>
<td>Left heart muscle &gt; TVs that open in the left side &gt; aorta and regional arteries</td>
</tr>
<tr>
<td>Pulmonary ET-1</td>
<td>Endocrine loop through systemic circulation</td>
<td>Lungs &gt; aorta and regional arteries</td>
</tr>
</tbody>
</table>

**Table 2. Possible, here proposed ET-1 mediated control loops that allow modulation of preload and afterload of both ventricles.**

Supraphysiological ET-1 exposure can damage organs and tissues (LV - left ventricle; RV - right ventricle).
The left atrium is exposed to two separate thrombospondin 1 sources, from lungs via pulmonary veins and from myocard via left atrial Thebesian veins. It can be presumed that in many pulmonary or cardiac patients, these two organs often secrete a surplus of TSP1, thus making TSP1 blood levels increased in the left heart, particularly in the left atrium. In short, this means that the left atrium and ventricle are only chambers that receive both pulmonary and myocardial TSP1.

A thin and TSP1-rich juxtamural layer of blood surrounding Thebesian veins can temporary form during the end-diastolic atrial and ventricular phases. In a normal heart this should not increase the risk of thrombus formation, since all secreted TSP1 will be quickly diluted by the inevitable systole that mixes all blood during ejection.

Here the proposed sequence of events starts with the onset of atrial fibrillation:

- Since there are no systoles to mix the atrial content, TSP1 is not adequately diluted and washed away from atrial cavities:
  - In the right atrium, systemic venous blood is poor in TSP1 and the buildup of cardiac TSP1 via CS and TVs depends on myocard stretching and endocrine factors. In many patients, the right atrial TSP1 levels probably remain well below the increased risk of thrombus formation.
  - In the left atrium, pulmonary disorders increase TSP1 levels in blood that enters from pulmonary veins. Dilated atrial walls continuously leak venous blood that contains myocardial TSP1. These two sources build up the juxtamural TSP1 concentration in the vicinity of the TVs openings, thus stratifying the juxtamural layer of blood in peripheral parts of the left atrium with TSP1.

- Blood carried TSP1 molecules that enter the fibrillating left atrium mimic actions of the platelet-derived TSP1 in promoting the thrombus formation. Increased local availability of TSP1 protects endothelium-bound and subendothelial von Willebrand factor from degradation by plasma ADAMTS13, as it has been reported for soluble or local platelet-released TSP1 in a shear field\(^2\). This TSP1 action, combined with stagnant blood flow in peripheral parts of the left atrium, secures platelet tethering, thrombus adherence and growth.

**Part V. How to prove the proposed interpretation of mRNA data**

Since levels of ET-1 and TSP1 in the peripheral vein is not expected to be adequately related to the pulmonary and coronary levels of these two mediators, here proposed interpretations can be tested by taking blood samples from other vascular segments.

One possibility is to measure ET-1 values in samples of blood taken during systole and diastole from the right atrium (near the coronary sinus) and from aorta (below the aortal valve):

- If ET-1 levels in the right atrial blood are lower than in aorta, or show inverse oscillations during the heart cycle, this would prove that Thebesian veins of the left heart side act as an important direct shortcut for ET-1 from the myocard to systemic arteries.

<table>
<thead>
<tr>
<th>Circulatory segments</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Right heart</strong></td>
<td></td>
</tr>
<tr>
<td>Veins of systemic circulation: blood</td>
<td>slow laminar flow under low pressure</td>
</tr>
<tr>
<td>contains little TSP1 in healthy individuals</td>
<td></td>
</tr>
<tr>
<td><strong>Left heart</strong></td>
<td></td>
</tr>
<tr>
<td>Pulmonary veins: blood contains TSP1</td>
<td>slow flow is interrupted by short atrial systoles (P-Q segments). In case of atrial fibrillation, peripheral layers of atrial blood can be stratified with TSP1. Local build up of TSP1 from pulmonary veins and TVs can make the left fibrillating atrium prone to thrombus formation.</td>
</tr>
<tr>
<td>proportional to lung morbidity</td>
<td></td>
</tr>
<tr>
<td><strong>Right atrium: coronary sinus and mural TVs add blood with some TSP1, proportional to myocard stretching</strong></td>
<td></td>
</tr>
<tr>
<td>Left atrium: mural TVs add blood containing cardiac TSP1</td>
<td></td>
</tr>
<tr>
<td><strong>Ventricles: mural TVs add blood with some TSP1</strong></td>
<td>Blood is mixed during ejection that lasts near 1/3 of the heart cycle</td>
</tr>
<tr>
<td><strong>Pulmonary arteries: blood contains some TSP1</strong></td>
<td>Well-mixed blood travel fast under pressure, not prone to spontaneous thrombus formation</td>
</tr>
<tr>
<td><strong>Aorta and systemic arteries: blood contains TSP1</strong></td>
<td></td>
</tr>
</tbody>
</table>

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Table 3. Proposed mechanisms behind increased risk of thrombus formation in the left atrium during atrial fibrillation due to increased exposure of the left heart to pulmonary and cardiac TSP1 (TVs - Thebesian veins).
On the other hand, it might be important to measure the TSP1 level in simultaneously taken samples of blood from a systemic artery and from a central vein:

- Higher TSP1 levels in the arterial blood are expected if pulmonary and myocardial TSP1 into circulation is increased due to disorders of these two organs, making the patient prone to peripheral artery embolisms in the case of atrial fibrillation.

- In the opposite case with higher TSP1 levels in central veins, the overall TSP1 leakage from peripheral tissues back to the heart is increased, possibly due to metabolic disorders or tumors and this setting increases the risk of thrombus formation in peripheral veins. This can be related to the Trousseau’s syndrome, associated with the pancreatic, gastric and lung cancer.

## Competing interests

The author declares not to have any competing interests regarding the content of this article.

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## References

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GENERAL COMMENTS:

This is a well-written, provocative ‘Opinion Article’ that uses, in part, published observations to propose a novel hypothesis concerning the roles of Endothelin 1 (ET1) and Thrombospondin 1 (TSP1) in circulatory regulation. A few logical inferences upon which the supposed relationships are predicated are not immediately clear to this reviewer, but this should be easily rectified. The author’s focus upon the regulatory role of substance delivery via Thebesian veins and via flow through the coronary sinus (in their role as a “bidirectional portal system”) is notable since, to my knowledge, these structures have received almost no attention in this context.

I confess to relative ignorance of the actions of ET1, but the pulmonary vasculature (or pulmonary smooth muscle) responds differently from the systemic in some circumstances. I asked two of my respiratory/pulmonary colleagues what the action of ET1 was in the pulmonary circulation, and neither knew. Please clarify ET1 effects on pulmonary (i.e., vs. systemic) at some appropriate point in this ms (i.e., affirm that ET1 vasoconstricts the pulmonary circulation).

The author uses the word ‘myocard’ rather than ‘myocardium’; the latter is common English usage in this reviewer’s experience, and his use of ‘myocard’ instead was a bit distracting. The author might want to consider changing his usage to ‘myocardium’ if (and only if) he considers it likely that the majority of his readers will be more familiar with ‘myocardium’.

SPECIFIC COMMENTS

- Abstract: The first of the uncertain logical links occurs in the first sentence of the abstract: it is unclear to me why ‘similar expression profiles’ necessarily implies that the two mediators are “dominantly synthesized in the myocard and lungs.” It is acceptable to me to leave this statement as is and clarify the logical link in the full text, but this is foundational to the author’s argument and should be sufficiently expanded to enhance clarity where most appropriate.

- Introduction: The opening sentence again ‘suggests’ dominant synthesis in myocard and lungs. I suggest that amplification here of this logical sequence would be the best and easiest place to make this clearer. If I’m missing something simple, I apologize! The first sentence of this next (2nd) paragraph probably needs a reference.
• p. 3, right column, para. 2: It was observed…: Please reference this observation.

• Table 1: This is a formidable table whose ‘message’ is difficult to ferret out; simplify if practical. (Note the error in middle column, row 1: <10 L/min.)

• In the sentence that introduces Table 1 the word ‘surplus’ (of myocardial mediators) is used; I’m not convinced that this word is appropriate: even if only modest amounts of mediator are secreted, must not some percentage pass through the TV and CS? (Likewise on p. 5, left column, para. 3.)

• P 4 (of 8), right column, 3rd paragraph: The antecedent of ‘it’ in the first sentence (…endocrine loops it can be expected…) is not clear to me. I assume ‘it’ is ET1 or TSP1, but, as written, ‘disorder’ would seem to be the antecedent.

• p. 5, left column, para. beginning “Table 1 is based…”: The ‘expectation’ that stretching of the myocardium (or dilation and thereby patency of the TV in the LV) increases synthesis is important to the author’s thesis; please reference or give some validation for this ‘expectation’.

• Next para: The intended meaning of the opening sentence (When considering…) is not clear.

• p. 5, top of right column: I admit to being a bit ‘picky’, but the use of ‘it’ (It is similar…) seems weak to me. Also, would ‘into’ not be better than ‘in’ here (…ET1 secreted into the left heart…)

• p. 5, last para: I do not understand what you mean by ‘repetitive’ in this opening sentence. Cyclic? (If so, I don’t think this would be correct.) My confusion is increased by the logical connection between this (repetitive changes) and the next sentence (tissue structure integrity and cellular interconnection dependent upon repetitive.) Please clarify.

• p. 6, “Disorders possibly…” paragraph: Would ‘produced by’ be better than ‘of’ so sentence might read “Table 2. Shows possible damage produced by supraphysiologic…”?

• p. 6, left column, final line: …the excess ET1 … reachES (not reach) lungs. In this second autocrine loop are you referring to a loop made via the TV which would exist in all people, but become functionally important in only certain patients (e.g., Eisenmenger’s syndrome)?

• (I found the proposed application of your concepts to thrombus formation in the LA to be particularly interesting, though at points somewhat harder to follow and integrate with Table 3.)

• p. 6, last para. introducing Table 3: Do you mean “As shown in the middle row, right column of Table 3…”? In other words, it would be helpful to the reader to ‘walk him through’ Table 3 a bit more in the text.

• p. 7, Part V: Consider replacing the word ‘prove’ with the word ‘test’. In the opening sentence of this section “Since levels of ET1 and TSP1 in the peripheral vein ARE not expected…”

Is the topic of the opinion article discussed accurately in the context of the current literature?  
Yes

Are all factual statements correct and adequately supported by citations?  
Partly
Are arguments sufficiently supported by evidence from the published literature?
Partly

Are the conclusions drawn balanced and justified on the basis of the presented arguments?
Yes

**Competing Interests:** No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.