
http://www.elsevier.com/locate/issn/03069877

http://www.sciencedirect.com/science/journal/03069877

http://dx.doi.org/10.1016/j.mehy.2015.08.001

http://medlib.mef.hr/2763
Type 5 and 6 nasal septal deformities: could we predict and prevent acute coronary syndrome attacks in the future?

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Summary

Undisturbed nasal breathing is essential for normal breathing physiology as a whole. Nasal septal deformities (NSD) are well known as a factor which can remarkably and substantially affect the quality of nasal and pulmonary breathing. However, it is well known that type 5 and type 6 nasal septal deformities may cause only a moderate, unilateral nasal obstruction or none at all. The effects of nasal obstruction on the respiratory and cardiovascular systems have been well studied so far: right ventricle problems, ischemic heart diseases, sleep disorders, mucociliary clearance system disturbances, paranasal sinus pathology, have all been described as a result of impaired nasal breathing. The connection between the upper and lower respiratory systems has been recognized in allergic rhinitis and asthma as well, resulting in the united airways concept. Most recently, the ostensible connection between chronic rhinosinusitis (CRS) and acute myocardial infarction has been said to be proven. However, the results of this study might have not been well founded since there are no direct and clear proofs that CRS as a chronic inflammatory process has anything to do with the acute coronary syndrome (ACS). On the other hand, a large international study on the incidence of NSD in CRS patients, based on the Mladina classification, showed that NSD were present in a high incidence and that the most frequent deformities were types 5 (36.18%) and 7 (29.92%). The vast majority of those types 7 consisted of types 3 and (again) types 5 or types 6 (76.32%). The fact that in CRS patients a remarkably high incidence of type 5 septal deformity can be seen, gives rise to thinking that this factor perhaps plays a role in the onset of ACS. Acute coronary syndrome is one of the leading causes of death all over the world. Traditional risk factors such as family history, overweight body, smoking, stress, hypertension, hypercholesterolemia, diabetes mellitus, coronary artery calcium score, C-reactive protein, lipoprotein, homocysteine, lipoprotein-associated phospholipase A2, as well as high-density lipoprotein functionality perhaps cannot account for the entire risk for incident coronary events. Several other potential risk factors have been identified in an effort to improve risk assessment for ACS. This article reviews one of them: the possible influence of an unusual, so far unknown predisposing factor: type 5 or type 6 nasal septal deformities. They have been found as pure, isolated types or as a part of combined nasal septal deformity (type 7).
Introduction

Undisturbed nasal breathing is essential for normal breathing physiology as a whole and the effects of nasal obstruction on the respiratory and cardiovascular systems have been well studied: right ventricle problems\(^{1,2}\), ischemic heart diseases\(^{3,4,5,6,7,8,9}\), sleep disorders\(^{10,11,12,13}\), mucociliary clearance system disturbances\(^{14,15}\), paranasal sinus pathology\(^{16,17}\), have all been described as a result of impaired nasal breathing. The connection between the upper and lower respiratory systems has been recognized in allergic rhinitis and asthma as well, resulting in united airways concept. A concept of treating the upper airway pathology in order to improve pathology of the lower airways and vice versa changed and improved treatment results. Surgical treatment of the nasal obstruction has a positive effect on pulmonary function tests\(^{18}\) and on quality of life in general\(^{19}\). Ogretmenoglu and his group showed that even light bilateral nasal packing has a strong influence on arterial blood gases and heart rate\(^{20}\). The connection between particular types of nasal septal deformities (NSD) and minimal cross-sectional area of the nasal cavity and body surface area has been confirmed ten years ago\(^{21}\). Most recently, the ostensible connection between chronic rhinosinusitis (CRS) and acute myocardial infarction has been proven\(^{22}\). Focal accumulation of fluids containing proinflammatory cytokines and altered activation of the coagulation system in the paranasal sinuses has been reported in CRS patients\(^{23, 24}\). Besides, some hypotheses proposed that exposure to these proinflammatory cytokines may trigger juxta-vascular inflammation and promote intravascular thromboses\(^{25}\), and that there is growing evidence which confirms that sleep-disordered breathing has direct proatherosclerotic effects and can exacerbate other cardiovascular risks\(^{26}\). But we have to exercise caution this holds a big trap: this study, like all others before it, makes no mention of nasal septal deformities in those patients. It does not mention any data regarding NSD in general, and furthermore, getting some idea about any of the particular types of NSD seems science fiction here! How is it possible to study patients suffering from CRS without mentioning any word on NSD or radiological findings? How reliable have all those CRS diagnoses been? Furthermore, it was obviously a retrospective matched-cohort study. For selection of the study cohort the authors first included 25673 subjects (!) who had received a first-time principal diagnosis of CRS. But who has given the diagnosis of CRS and how? This, of course, is not at all acceptable for any contemporary
rhinologist. At the same time, to discuss an acute myocardial infarction without mentioning a coronarography finding is unacceptable for contemporary cardiologists. However, rhinologists are very well aware that CRS patients mentioned in this study have certainly had some septal deformity. Most recently, a large international study based on Mladina classification, proved this statement. It showed that the most frequent NSD among patients suffering from CRS were types 5 (36.18%) and 7 (29.92%) and, in addition, it was found that the vast majority of those types 7 consisted of types 3 and, again, types 5 (76.32%). The rest were represented by other, pure types of deformities such as: type 1 showed up in only 1.53%, type 2 in 3.05%, type 3 in 21.63, type 4 in 6.15% and type 6 in only 1.53%. Within this list of pure nasal septal deformities (i.e. isolated ones, not combined among themselves), type 3 has been found in more than one fifth of all! Already, at very first sight, it seems logical to expect type 3 in CRS patients: this type means vertical septal deflection at the borderline between perpendicular and quadrangular lamina, which produces unilateral narrowness of the nasal cavity resulting in distortion of physiologic laminar airstream into turbulent streams which produce essential change of the normal respiratory epithelium into multilayer squamous cell epithelium with no more cilia and mucociliary transport system. The mucociliary transport system is mandatory for the maintenance of healthy sinuses. The opposite, larger nasal cavity is not physiological either, since laminar airstream looses the maintenance from the septum, and, like in the narrow side, turns from laminar into turbulent streams as well. The result is the same: CRS. There is, however, another detail that has not been adequately emphasized but offers the answer to the enigma of the hypothetic influence of CRS on the acute coronary syndrome (ACS): type 5 NSD has been found as a pure type in 36.18% and as a part of type 7 in 76.32% of CRS cases! The impact of the nasal obstruction and particular types of NSD to the cardiac pathology has obviously not been well studied yet, despite the fact that there is growing evidence that upper airway obstruction, on which NSD have an expected, profound influence, has a negative effect on cardiac function! The problem lies in the fact that none of the studies that investigated the relationship between the upper airway obstruction and cardiac function offered a systemic approach to the definition of the “upper airway obstruction”. What does it mean, this famous term? A nose full of polyps? A bilateral nasal septal deformity? A big antrochoanal polyp? An advanced vasomotor rhinopathy?
The lack of this data in the “Material and methods” sections of the previous studies gives rise to the general mess in the interpretation of the results obtained so far. We still do not have a clear idea who or what exactly could be the rhinologic culprit (if any) for breakdowns in the cardiac system. Who or what exactly could be blamed for heart failure of whichever degree and type in cases of so called “upper airway obstruction”?

Nasal septal deformities are well known as a factor that can remarkably and substantially affect the quality of nasal and pulmonary breathing. The etiology of the deformities is multifactorial, with trauma and genetics as leading factors27, 28. Nasal septal deformities appear in various forms, but there is still an obvious difference between particular types. This was first suggested and described by Mladina29. He defined seven types of NSD: four vertical (types 1 - 4), two horizontal (types 5 and 6) and their combination, i.e. type 7 (Figures. 1-5). Type 7 presents a combination of the previous types always following the same rule: one of the four vertical types is combined with type 5 or type 6, or, in extreme cases, with both of them. Because of this, every single type 7 is also very well defined.

The incidence of NSD changes with age. Regarding children and adolescents (2-22 yrs of age), the study by Šubarić and al.30 showed that the general incidence of nasal septal deformities was 28.9%, and the most frequent types of nasal septal deformities were types 1 (14.7%) and 2 (6.8%). Types 5 and 6 appeared in only 2.9% and 2.6%.

Mladina and his group managed to show that the general incidence of NSD in adults was remarkably higher, i.e. almost 90%31. The most frequent types found were type 3 (20.4%), type 2 (16.4%), type 1 (16.2%) and type 5, which appeared in 14% of investigated subjects. Type 6, however, was found in only 9.4% of them. According to these facts, the aggregate incidence of the incriminated two types (5 and 6) would be around 24.4% in the general ENT population in adults.

Provided that the influence of NSD to the cardiac pathology is really so strong and fatal, almost 90% of the adult population in this world would be cardiac patients, which, fortunately, is not true at all. This gave a rise to the idea that maybe only some specific types of NSD have something to do with both the so called “upper airway obstruction” and/or cardiac function. But, if that is the case, what is the magic?
It seems the magic is very simple: pure types 5 and 6, or type 7 which always consists of at least one of those two, flaringly dominate over other types of nasal septal deformities in patients who survived an ACS and later on showed a positive coronarography.

ACS patients with a negative coronarography showed a predomination of vertical NSD like types 1, 2, 3 and 4 (78.34%). This finding suggests that types 5 and 6 should be treated as a warning sign, the whistleblowers, that could alert doctors that their patient belongs to the group of people with a certain degree of predilection for the onset of ACS with positive coronarography. Thus, a hypothetic question arises here on whether horizontal deformities, i.e. types 5 and 6, play some role in the onset of ACS followed by positive coronarography or not? And, if yes, the much more important question is: what is the acting mechanism? Do they obstruct the nasal airway substantially, thus producing well known consequences regarding the heart function as it was stated so many times in literature so far, and most recently under the well known syntagm of obstructive sleep apnea syndrome (OSAS)?

Numerous rhinomanometric studies have shown that vertical and horizontal nasal septal deformities contribute equally to the degree of impaired nasal breathing\textsuperscript{16}. Unfortunately, again, none of these studies have been based on the Mladina classification, i.e. they terribly lack standardization in terms of “septal deviations”. That is why we cannot predicate that some of seven Mladina NSD types are the “rhinomanometric champions” and fateful for seriously impaired nasal breathing and health problems connected to this hypothetic “nasal obstruction” solution. Looking at it theoretically and logically, one could expect, in the case of a flaringly emphasized type 5 staying in more than close contact to the lateral nasal wall, a notable, but still only unilateral nasal obstruction. The same could be said of vertical deformities, like types 2 and 3, while only type 4 could, in emphasized cases, produce bilateral, real nasal obstruction. A pure type 6, in most of the cases, does not essentially influence the quality of nasal breathing.

This would mean that perhaps, aside from the inherited appearance of the nasal septum in a particular individual, there is also an inherited affinity to the development of serious cardiac pathology accompanied by a positive coronarography. In terms of
this, a meticulous anterior rhinoscopy as well as fiber-endoscopy of the nose should be added to the schedule of preventive cardiac examinations and tests.

What is the future?

In the future we need help from molecular biologists. Why? Because most probably there are some gene aberrations responsible for the onset of both types 5 and 6, and perhaps, at the same time, the same ones are responsible for the predisposition to the onset of ACS with positive coronaryography finding. As we know, ACS happens to both those carrying types 5 or 6 and those who do not. The only difference is the positive coronaryography in those carrying types 5 and 6, which means those with more severely damaged heart. We could presume that perhaps types 5 and 6 are just a balance cock: if one has type 5 or 6 nasal septal deformities, he or she could be more inclined to the onset of severe heart failure with the positive coronaryography finding. If ACS and types 5 and 6 belong to the same gene family, ACS could be prevented due to future possibilities of gene therapy which will be able to eliminate the “bad guys” from the gene and thus eliminate the possibility of developing an ACS before it happens. Great hope regarding this appeared on the horizon very recently: A Chinese group of molecular biologists lead by Liang succeeded for the first time in human history to edit the genes of a human embryo. The researchers from Sun Yat-Sen University in Guangzhou reportedly used the CRISPR/Cas9 technique to knock out a gene called HBB out of donor embryos, which causes the fatal blood disorder β-thalassaemia. This marks the first time that the CRISPR technique has been employed on an embryonic human genome. The Chinese colleagues found a way to prevent thalassemia in the embryonic stage, changing the gene structure in parents.

In this case, all well known traditional risk factors such as family history, overweight body, smoking, stress, hypertension, hypercholesterolemia, diabetes mellitus, coronary artery calcium score, C-reactive protein, lipoprotein, homocysteine, lipoprotein-associated phospholipase A2, as well as high-density lipoprotein functionality, cannot account for the entire risk for incident coronary events. The fiber
endoscopic examination of the nose, searching for type 5 or type 6 nasal septal deformities, will be added to the schedule of preventive cardiac examinations and tests. If so, they will be able to change human future: the number of heart failure caused deaths (like ACS) will dramatically decrease owing to the future possibilities of the gene therapy. Cardiovascular diseases (CVD) are now the leading cause of death worldwide. It continues to be on the rise and has become a true pandemic that has no respect for borders. Coronary artery disease is the most common type of CVD. It continues to be the leading cause of mortality both in men and women in the U.S. Approximately every 25 seconds, an American will suffer an acute coronary syndrome, and approximately every minute someone will die of one. In France, they are responsible for 142,000 deaths every year. In terms of these data, human life in general could be substantially prolonged.

In short, here are our hypotheses:

1) There is a gene responsible for the development of type 5 and 6 nasal septal deformities.

2) Since type 5 and 6 nasal septal deformities are flaringly frequent among patients who survived an ACS and showed positive coronaryography finding, perhaps ACS with the positive coronaryography and types 5 and 6 belong to the same gene family.

3) ACS with the positive coronaryography could be predicted in individuals carrying one or both of these types.

4) In the years to come, the ACS with the positive coronaryography finding could be also prevented owing to expected future possibilities of gene therapy which will be able to knock out the “bad guys” from the gene(s) and thus eliminate the possibility of developing an ACS before it happens.

5) If so, molecular biologists will be able to change human future: the number of heart failure caused deaths will hopefully dramatically decrease and human life in general will be substantially prolonged;
6) Anterior rhinoscopy regarding the search for the possible existence of type 6 and nasal endoscopy as the safest way to diagnose the existence of type 5 will be added to the schedule of preventive cardiac examinations and tests.

Conflicts of Interest statement

We declare that there is not any potential conflict of interest or any source of funding.
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Figures legends:

Fig. 1. A left sided type 3 septal deformity. S-septum, IT-inferior turbinate, arrow-middle turbinate
Fig. 2. Right nasal septal deformity during the native anterior rhinoscopy. The vast majority of the deformity is hidden by the head of the inferior turbinate. S-septum, IT-inferior turbinate

Fig. 3. Right nasal septal deformity after decongestion. The type 5 has been clearly identified (0° rigid endoscope view) S-septum.
Fig. 4. Native anterior rhinoscopy presenting the left-sided type 2 septal deformity. S-septum, IT-inferior turbinate

Fig. 5 A). A native rhinoscopic view to the left-sided type 6 septal deformity. B) The typical gutter (white arrow) determines the side of the deformity which is entered into the documentation. IMBW- intermaxillary bone wing, PSE-palatal septal edge that has slipped into the right nasal cavity, out of the medial plane, LMT- left middle turbinate, RIT- right inferior turbinate.