HYPOXÆMIA TESTS IN CORONARY DISEASE

BY

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Many people have suffered from anginal pain and have still lived to old age. Cardiac infarction may set in suddenly after having been for a long time foreboded by a typical angina pectoris: on the other hand, a person may without any warning whatever fall prey to a lethal infarct. The dramatic character of the picture of the coronary heart disease and its capricious appearance raise the following two questions. How can one make an early diagnosis on the basis of the changes that form the substratum of the disease in order to permit a timely recourse to prophylactic measures? Can refined diagnostic measures dispel the anguish many people feel owing to the dread of this disease? Apart from electrocardiograms common clinical examination is not of much use. The history is the chief factor, but people differ in sensitivity to pain, in the faculty of observation, and in exactness of description. No wonder that attempts have for a long time been made to create a practical and objective method of testing the coronary function. Two principles have been applied in the first place, viz. electrocardiograms after respiration of air lacking in oxygen (by a gas mixture with diminished oxygen pressure or general under pressure), and after exertion.

Since the former method, referred to as the “hypoxæmia* test” by us, has now been employed for more than three years, it has seemed desirable to submit a few preliminary figures collected during the years 1942–44, to supplement the experiences so far available of the test as a practical method in clinical work. For reasons of space, I must limit myself to a statement of the figures without further critical remarks except the most necessary ones.

In 1933, Dietrich and Schwiegk found pathological features in the cardiogram after breathing air deficient in oxygen. Kai Larsen (1938) at Warburg’s clinic in Copenhagen, performed 192 hypoxæmia tests on 133 subjects, 28 of whom were healthy and 43 suspected of coronary heart disease. The oxygen percentage in the inspiration air was 9 per cent, the test lasting for 6–8 minutes. As regards cases with coronary symptoms, he found 4 positive tests in 10 instances with a normal cardiogram at rest and 5 positive tests in 10 others with but small changes in the cardiogram at rest; in another 4 cases in the latter group, a positive cardiogram with exertion was noted. In the U.S.A., Levy, Barach, and Bruenn (1938) gave an account of their first investigations regarding the effect of hypoxæmia on the circulation. The work was supplemented in 1940 by Levy, Bruenn, and Williams with studies of the effect of drugs during hypoxæmia tests. Those studies were pursued in 1941 by reports from Levy, Bruenn, Williams, and Carr on 326 tests with 10 per cent oxygen for 20 minutes in 262 cases, 115 of whom were healthy and 147 suffered from cardiac disease, 79 of the latter having suspected or certain coronary heart disease. They obtained from 18 to 69 per cent positive tests, relative to the degree of the coronary symptoms and the appearance of the cardiogram at rest.

In Sweden, Nylin (1943) has earlier presented some data from 163 private patients with 22 per cent positive tests. Åkesson and Malmström (1945) have recently published some cases of cardiograms after exertion when breathing air deficient in oxygen. The hypoxæmia test in one form or another has also been adopted for clinical purposes elsewhere in this country.

* The term hypoxæmia has been used throughout instead of anoxæmia, which is most common in the Anglo-Saxon literature, because the former has been considered more adequate in this connection.
METHODS AND GROUPING OF PATIENTS

The material which will be discussed in the present paper comprises 350 hypoxæmia tests carried out on a total of 326 patients examined during the years 1942-44 at the Sabbatsbergs Sjukhus: 166 of these patients were men and 160 women; 43 of the total number of patients were under 30 years of age, 40 between 31-40, 88 between 41-50, 88 between 51-60, 54 between 61-70, and 13 above 70 years of age. In 1942, 87 cases were examined, 8 being positive, i.e. 9 per cent, and in 1943, 140 cases, 20 being positive, i.e. 14 per cent, and in 1944, 114 cases with 20 positive tests, i.e. 17 per cent. The indications for the use of the test have probably been gradually stabilized.

The technique employed here conforms to that adopted by Levy et al. (1938, 1940) viz. inspiration of a mixture of 10 per cent oxygen and 90 per cent nitrogen for 20 minutes. Nylin has described the details earlier. The patient, who has not eaten for some hours, is placed on an examination couch and inhales the gas compound through a mouthpiece connected with a Lovén mask while a nose clip is adapted. The patient is informed of the nature of the test, of the discomforts that may appear, and requested to breathe calmly and give a signal with the hand to the assistant if the discomforts should become too severe. A cardiogram is taken at rest before the test and after 20 minutes or earlier if the test should have to be abbreviated. Immediately after the test, the patient is given 100 per cent oxygen-gas for as long as necessary.

The gas mixture was delivered during the first years in bombs containing 10 per cent O₂ and 90 per cent N₂. According to analyses which have been performed, the oxygen content has varied within the limits 10±0.3 per cent. During the second half of the year 1944, the gas-mixture bomb was replaced by a gas-mixing apparatus, constructed at Aga by Andersson, civil engineer, according to Nylin’s directions, the principle of which will be seen in the diagram (Fig. 1). Pure nitrogen gas runs through an injector (3) into a gas current-meter (5)

![Diagram of gas-mixing apparatus](http://heart.bmj.com/)

which draws in by means of suction a quantity of indoor air (8) which can be made equal to the nitrogen gas quantity by manipulation of the floats (4, 7) in the two gas current-meters. Since the hypoxæmia tests are performed in fresh indoor air with an oxygen content of 20 per cent, the oxygen-gas content in the gas mixture will, accordingly, be half of it, i.e.
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**TABLE I**

**DETAILS OF HYPOXEMIA TESTS (1942-44)**

Number of tests, 350.

**cor. dis. = coronary disease.**

A.P. = angina pectoris.
10 per cent. The oxygen-gas content obtained by this method will be at least equal in reliability to a ready mixture.

The cardiogram examined has, in practically all cases, also comprised one or several chest leads. In the course of these years, different chest lead procedures have been tried at the clinic. The predominant number of cardiograms have been performed with Nylin's anterior and posterior lead, some also with an inferior lead, as described earlier by Nylin and Grewin (1942). After the stabilization of the chest lead technique to only the anterior and posterior leads, all the five leads have been registered synchronously with the help of Elmqvist's five-lead electrocardiograph.

The indications for the hypoxämia test have principally occurred in the following cases: suspected coronary cases, a mixed group of undifferentiated cases sent to our clinic for an estimation of the possible risks of operation, and cases from the State Insurance Board. The test has been regarded as contra-indicated in the event of infarcts within six months and in cases with failure. Nor has any patient been subjected to more than one test on one and the same day.

The earlier discussion dealt with, _inter alia_, the risks involved in the test. In this instance, experience has however been favourable. The majority of patients manifest, during the course of the test, a considerable general cyanosis. The deficiency in the oxygen saturation of the blood, as a rule, raises the frequency in the heart of, probably, about 25–40 per cent. Many patients, in fact, feel a moderately severe headache. Thus, these occurrences are to be expected and need not give rise to anxiety in the patient or the conductor of the test. Further, they are rapidly transient when the oxygen-gas has been turned on at the end of the test. As to the possibility of complications, two have occurred in our material, viz. firstly, mild anxiety in very nervous patients, and secondly, attacks of paleness, peripheral chill, bradycardia, sensation of choking, and general appearance of shock. In all likelihood, this is due to a vagal excitation in persons particularly predisposed to it. No technical error has been noted. Recently, two alarming cases of this kind have been observed, but no effect on the cardiogram other than bradycardia was detected. Both cases recovered quickly by means of adequate therapy. In this material a similar picture seems to have occurred in one case, also with a negative result of the test, but, on the other hand, with suspected anginal pains. The cases with a decrease in the heart frequency after 20 minutes may, perhaps, be milder equivalents to the forementioned case. They comprise another 13 with negative tests and one with a positive test. Thirdly, there may, conceivably, involve a risk of eliciting an infarct in a heart where this constitutes a latent threat. We have not been in a position to ascertain any such case, nor have I seen any mention of it in reports on the subject. On the other hand, suspected or typical anginal pains have appeared in 7 cases with positive tests, 6 of which have been interrupted after less than 20 minutes, and in 5 negative cases, 3 of which were interrupted prematurely. Infarction has not ensued from the test in any single case. An infarct was mentioned in the patient's history in one of the positive cases and in one of the negative ones which was interrupted prematurely. According to a newspaper notice, one patient died 13 days after an attempt to perform a hypoxämia test which had had to be interrupted owing to pain without the registration of any curves. He had suffered from an anterior infarct two years earlier and had been incapable of work for a year on account of pain.

Apart from the first acute stage of a cardiac infarct, the coronary heart disease is more frequently, at the time of the examination, a latent condition than a manifest one. Thus the _raison d'être_ of a hypoxämia test should be to confirm or remove, objectively and manifestly, any suspicion of the coronary heart disease that there has been reason to entertain on the basis of the patient's history.

Taking this into consideration, the present material has been classified in accordance with the patient's history and such simple clinical data as can be established by any physician, and not according to the clinical diagnosis arrived at after examination of the cardiogram and hypoxämia tests of the patients concerned. Moreover, when the aim has been to "expose" a latent injury, in a cardiographic respect, a differentiation between the various tests has seemed most adequate in accordance with the appearance of the ordinary curve at rest. As regards the usefulness of the test compared with the ordinary cardiogram, a patho-
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logical test after a normal ordinary record is of more importance than an accentuation of the curve of coronary insufficiency. The tests have therefore been divided into 4 groups, as follows: one with a normal cardiogram at rest, one with a coronary curve at rest, another with a "cardiosclerotic" curve at rest (bundle branch block, low voltage), and, finally, one with some other change in the cardiogram at rest (principally arrhythmias). The test has been denoted as negative, doubtful, or positive, according to the outcome of the test. For practical reasons the following criteria of Levy et al. (1941) have been used with, however, a substitution of lead IVF for one of our chest leads.

Criteria for Positive Tests, according to Levy et al. (1941)

The test is positive when
1. the lowering of the S-T segments in leads I, II, III, and IVF constitutes or exceeds 3 mm., or
2. T I is inverted, altogether or partly, and the S-T segment in lead I is lowered at least 1 mm., or
3. T IV is altogether inverted, irrespective of the S-T segment, or
4. T IV is partly inverted and the S-T segment is lowered at least 1 mm.

Clearly affected tests, not fitting into Levy's scheme, have been referred to a "doubtful" group. Still, the exact tracing of the limits between these groups remains an open question which future follow-up examinations may solve. No definite patho-physiological quantitative correlation to the positive test is as yet known. On the contrary, Vesa's observations as well as our own have shown that considerable spontaneous variations occur on and off with regard to S-T segments and T waves. There is, reasonably, no cause to believe that a certain limit at all exists. The transitions are, probably, vague and therefore a separate group of doubtful tests may, for the time being, be justified, not least in consideration of later follow-up examinations.

The cardiograms have chiefly been studied only with regard to the S-T segments and the T waves. The distance from the extreme points of these parts of the curve to a horizontal line through the lowest level of the P-Q line has been measured within 0.5 mm.† Hypoxæmia tests cannot be estimated without millimetre measurement.

In order to be able to perform off-hand an arrangement of each case in the most correct clinical group with the guidance of the history of the patient and simple clinical data (with the exception of the cardiogram), extracts from the records in this respect have been made on one side of a so-called needle-card, while the cardiographic facts have been annotated on the back. Then, the whole material has been classified simultaneously in order to obtain the greatest possible uniformity. The clinical group has been marked on each card before turning it to analyse the cardiographic changes.

The clinical grouping has been intended to comprise the following cases:
(1) Somatically healthy persons.
(2) Cases of another disease (often consultation cases).
(3) Cases of organic heart disease (valvular diseases and endocarditis or myocarditis.)
(4) Cases of hypertonias.
(5) Cases of other heart diseases (principally arrhythmias, thyrotoxicosis, etc.).
(6) Cases with symptoms of angina pectoris, without any other disease.
(7) Cases with earlier cardiac infarct.
(8) Cases with later cardiac infarct (5 cases included in other groups).

The groups 2–5 have been divided into sub-groups with regard to the presence or absence, respectively, of "coronary" symptoms (mainly anginal pains), the latter being denoted as "suspected" or "probable" according to the degree of severity of the symptoms. Group 6 has, almost analogously, been divided into a group with symptoms resembling angina

* This group has also comprised curves with a digitalis effect or coronary insufficiency or both.
† It would, of course, be ideal to refer to a horizontal line through the T-P line which constitutes the real iso-electrical line. However, for technical reasons, Larsen as well as Levy, and others, have had to use the P-Q distance as a starting-point for the measurements. This has also been necessary in the present material of curves.
pectoris, but with a very faint suspicion of it, one with more suspicious symptoms, and another group with certain symptoms of what is called angina pectoris. The infarcts in group 7 have been classified according to the appearance of angina pectoris in the after-course.

The distribution of the material may be seen from the table.

**RESULTS**

The number of positive tests within each individual disease group seems to increase greatly according to the degree of clinical suspicion of the coronary heart disease.

When the whole material is distributed in the same way as the above-mentioned disease groups, the group where no (noteworthy) suspicion of a coronary heart disease occurs will have positive tests in 3 per cent of the cases, the group with suspected coronary heart disease will have positive tests in 20 per cent, and the group with probable or certain coronary heart disease in 30 per cent. When the cases which revealed coronary cardiographic changes already at rest are excluded from the calculation, the "exposing" hypoxæmia tests are obtained where the corresponding percentages equal 2, 18, and 23.

The cases with a pathological effect (positive tests) within the group with coronary curve at rest will analogously amount to 4, 27, and 40 per cent.

The four cases in which the test turned out to be positive without any suspicion of a coronary heart disease comprised a man of 56 years with pulmonary emphysema and chronic bronchitis, a woman of 36 years with recently alleviated acute myocarditis and 2 women of 53 and 57 years respectively, with hypertension but no symptoms of angina.

Only 5 of the 18 cases with earlier infarction gave positive tests, all of which were still suffering from angina, while 13 cases gave negative or doubtful tests (the latter in 3 instances), 11 with and 2 without angina pectoris.

Seventeen of the 166 men disclosed positive tests, the corresponding figures for the women being 27 out of 160. The percentage distribution of male and female positive tests within the three main groups is, in group I, 1 and 5 respectively, in group II, 14 and 23 respectively, and in group III, 28 and 36 respectively.

When the total material is distributed according to age, the group under 30 years offers 16 per cent of cases with positive tests, the remaining groups being as follows: between 31–40 years 15 per cent, between 41–50 years 7 per cent, between 51–60 years 18 per cent, between 61–70 years 11 per cent, and above 70 years 23 per cent. It is remarkable that 7 cases out of 43 have had positive tests under the age of 30. They comprise a man of 29 years with hypercholesterinaemia and infarction later in the course of the disease, a woman of 16, and one of 21 years shortly after an acute myocarditis, 2 women of 22 and 27 years, respectively, with paroxysmal tachycardia, a woman of 22 without definite diagnosis (high sedimentation rate (Westergren)), and a woman of 24 with exogenous psychosis and sensations of fear.

When the material is distributed according to professions, a distinction being made between heavy and less heavy work, and a more indefinite group of housework, the percentage figure of positive tests will be 10, 13, and 17 per cent respectively.

When an enlargement of the heart is considered to occur, i.e. when the radiological volume of the heart exceeds 500 c.c./m.² of body surface, among 18 cases with an enlarged heart in group I none had a positive hypoxæmia test, while 4 among 13 cases were positive in group II, i.e. 31 per cent. This also applies to 4 out of 8 cases in group III, i.e. 50 per cent. The corresponding figures, with regard to the cases with hearts of normal size in the several groups, were 3, 20, and 23 per cent respectively.

As regards cases with pulmonary disease and probably diminished pulmonary function, 1 out of 8 in group I and 1 out of 6 in group II had positive hypoxæmia tests.

* It is, of course, sometimes difficult to distinguish between coronary curves and those affected by digitalis. Eleven of the cardiograms denoted as coronary have been performed at a time when the patient had been given digitalis. It is doubtful in 4 cases whether earlier digitalis medication has as yet left any signs in the cardiograms. Thus, a possibility of digitalis influence has occurred only in 1 of the positive tests, 3 of the doubtful ones, and in 7 of the negative ones. Therefore, broadly speaking after considering the cases involved, a digitalis influence may be said not to be of any statistical significance in this material. When occurring, it must involve a slight increase in the percentage of positive tests at coronary cardiograms as compared with the figures stated above.
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As already mentioned, 15 cases showed a decrease in the heart frequency after the test. Another 14, one of which later became positive, obtained a cardiographic improvement of the curve as compared with the cardiogram at rest.

So far 12 patients have been reported to have died. Two of them gave positive tests. One was found at autopsy to have a considerable coronary sclerosis as well as recent thrombosis. The other was not subjected to autopsy but had died within an hour in an anginal attack. One case with a doubtful test revealed at autopsy much dilatation of the right half of the heart but no coronary sclerosis. Two out of 8 cases with negative tests had coronary cardiograms at rest, unaffected by the test. One of them was examined post-mortem and showed extremely narrowed coronary vessels, the other died of an infarct 4 months after the test. Two cases had “cardiosclerotic” curve at rest. One of them showed, at autopsy, hypertrophy and dilatation of the heart, as well as moderate coronary sclerosis. The other died suddenly on the operation table after finished surgical intervention. No autopsy was performed. One patient with a normal cardiogram at rest had very slight coronary sclerosis and was considered to have died of an Adams-Stokes attack. Two have died of decompensated mitral valve disease. One was examined post-mortem and revealed a typical mitral heart but no narrowing of the coronary vessels. One patient died of pulmonary carcinoma and was not subjected to autopsy. Finally, one patient died at home 13 days after the test; he had earlier had an infarct and suffered such severe pains at the test as to necessitate its interruption without any registration of the curve: as far as is known, no autopsy was performed.

A positive test has later become negative in 4 instances. This has happened in the following cases: a man of 52 years with Bürger’s disease, and another man of 67 years with certain angina pectoris, possibly with earlier infarction, who died later of a second infarct, as well as 2 women of 22 years of age, one with paroxysmal tachycardia and the other with no definite diagnosis. In the latter case the test improved parallel to the sedimentation rate and the clinical picture.

Exertion tests have been carried out in not quite a third of the number of cases, usually at the same pace as has been endured by the patient at the function test according to Nylin. These tests have often seemed difficult to judge on account of the tachycardia. When the tests, in which one S–T segment has been lowered to 1 mm. or more, or a T wave has been inverted (probably a very liberal interpretation) are regarded as positive tests, 16 out of 98 have turned out positive. The exertion cardiogram has been positive in 11 cases, while the hypoxæmia test has been negative, the condition being reversed in two instances. These figures do not, as yet, permit the drawing of any conclusions. However, it is possible that the hypoxæmia test and the exertion test affect the myocardium in different ways.

DISCUSSION

Larsen’s investigations have been performed on the basis of a different method. Levy et al. have, in their clinical classification, also taken into account the appearance of the cardiogram at rest. My figures cannot, therefore, be directly comparable to those obtained by them. However, the figure 20 per cent of positive tests for the whole of group II should correspond approximately to Levy’s 18 per cent. Further, the figure 40 per cent in my material should answer to Levy’s 55 per cent of positive tests at coronary sclerosis with angina and an abnormal cardiogram.

Finally, the question arises whether the results will repay the extra work and risks entailed in the method. The answer, of course, partly depends on the importance attached to the prognostic value of the positive hypoxæmia test. Is the artificial electrocardiographic coronary insufficiency, which may be in some cases brought about, a manifestation of a deteriorated coronary circulation and reserve even under physiological conditions? Levy describes a positive case where the autopsy revealed coronary sclerosis, and another case where death ensued owing to an infarct. The same applies in our material to the two positive cases where death has been reported. So far the material has been too restricted for critical conclusions but does, nevertheless, offer some indications. Also the question remains open whether it is less dangerous for a patient with angina pectoris to have a negative test than a
positive one. For the time being, care is advised in drawing conclusions from negative tests. In my opinion, the test has much to offer, for the diagnostic methods hitherto employed in this disease are inadequate and in urgent need of effective additions.

Finally, attention should be directed to future potentialities. The hypoxæmia test appears to "expose" several coronary cases which escaped notice at the simple cardiogram at rest. The same may apply, nevertheless, also to one or two cases which are not coronary in the actual sense. Still other coronary cases may escape notice at the hypoxæmia test. What is the reason for the varying outcome of the test? What factors play a part in this respect at the exchange of gas in the lungs, the heart and, perhaps, also in the central nervous system? The question may be asked, whether a local or general occurrence of the anatomical or functional insufficiency determines the electrical manifestation of the myocardial reaction towards the hypoxæmia stimulation. Such problems and many others in addition remain to be solved. The answer must be the outcome of various contributions from animal experiments, studies of autopsy material, and modifications and improvements of the technique. The latter refers, inter alia, to the discovery of the most suitable oxygen pressure in the gas mixture and control of the arterial oxygen saturation and the pH of the blood during the tests (which is certainly not the same in different patients according, i.e., to their technique of breathing).

**SUMMARY AND CONCLUSIONS**

After a brief retrospect of earlier examinations, a report is given of the particular technique used in hypoxæmia tests at the Sabbatsberg Sjukhus. The results obtained from 350 tests on 326 patients during the period 1942–44 are demonstrated. The number of positive tests is found to increase pronouncedly in accordance with the degree of clinical suspicion of a coronary heart disease. Thus, positive tests occur in only 3 per cent in the group without a suspected coronary disease, the percentage in the group with suspected coronary disease being 20, and in the group with probable or certain coronary disease 30. The material has also been analysed in several other important aspects. Finally, various possibilities for improving this part of the coronary diagnosis are discussed.

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