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Re·FLECTIONS

RGA's Medical Underwriting Newsletter

LETTER FROM THE EDITOR

Dear Readers:

In this edition of *Re-flections* the diversity found in life insurance medical underwriting is demonstrated through discussion of both a very common condition seen by underwriters, as well as a relatively rare impairment. The first article, "Weighing-in On Obesity", considers the mortality risk associated with obesity from a different perspective than is typically presented in the popular media. The second article, "Underwriting Pulmonary Hypertension", provides insightful guidance on dealing with the abnormalities of pulmonary arterial pressures noted on echocardiogram reports.

I hope that you will find both articles worthwhile and enjoyable.

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WEIGHING-IN ON OBESITY

by J. Carl Holowaty, M.D.

While obesity has always been a condition of human existence, and has certainly been accepted as a mortality concern in underwriting for quite some time now, there has been considerable media attention given to it over the last few years, providing an impetus to re-examine our current knowledge of the risk associated with this condition.

Although the incidence of obesity has been on the rise in most developed countries for some time, the current interest in obesity can be traced back to a March, 2004 report from the Center for Disease Control (CDC) in Atlanta suggesting that "Poor diet/Physical inactivity" was about to overtake smoking as the number one actual cause of death in the United States. While the report did not specifically identify obesity, the inference was that poor diet and physical inactivity led to deaths secondary to diseases such as cardiovascular disease. Many readers assumed that these deaths were directly attributable to obesity, and tended to disregard the issue of physical inactivity as a separate contributory factor.

The total number of deaths attributed to Poor diet/Physical inactivity in 2000 was 400,000. The data behind this report was published in the Journal of the American Medical Association (JAMA) in March, 2004. The media capitalized on the suggestion that obesity was to blame for these deaths. A subsequent article in JAMA in January, 2005 lowered the estimate of the deaths attributed to Poor diet/Physical inactivity. Finally, in April 2005, the CDC published information stating that "There were 112,000 more deaths than expected in [the year] 2000 among obese individuals…", and that "among the obese, the increased risk of death was most pronounced among people younger than 70." The CDC did not refer to activity levels or specifics of diet.

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Regardless of the actual number of deaths attributed to obesity, it is vital to understand the relationship between mortality and increasing degrees of obesity; to delineate the relative proportion of the population that is obese and to understand the disease conditions associated with obesity. These considerations are vital to not only the underwriting of the obese applicant, but also the pricing of insurance.

What is Obesity?

Obesity is clinically defined as a body mass index (BMI) of greater than 30, where BMI is defined as a relationship between a person's weight and height (in kilograms and meters). BMI=weight/height^2. This relationship allows the scientific community to use a universally accepted measure of build to evaluate the relationship between build and mortality. It also allows for people of different heights, but similar BMI, to be placed together into a similar risk pool. While the use of BMI is currently accepted as a valid way of assessing the risks associated with build, it lacks some of the refinements available to underwriters, such as waist circumference and the waist-hip ratio.

The current classification of obesity is:

Classification of Overweight and Obesity by BMI, Waist Circumference, and Associated Disease Risk

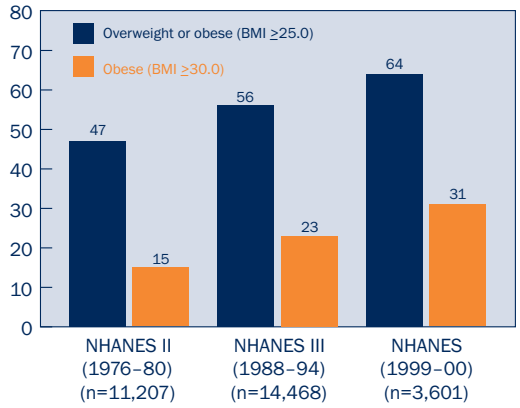
	BMI (kg/m2)	Obesity Class	Disease Risk* (Relative to Normal Weight and Waist Circumference)	
			Men ≤40in (≤102cm) Women ≤35in (≤88cm)	>40in (>102cm) >35in (>88cm)
Underweight	<18.5		—	—
Normal**	18.5–24.9		—	—
Overweight	25.0–29.9		Increased	High
Obesity	30.0–34.9 35.0–39.9	I II	High Very High	Very High Very High
Extreme Obesity	≥40	III	Extremely High	Extremely High

* Disease risk for type 2 diabetes, hypertension, and CVD.
** Increased waist circumference can also be a marker for increased risk even in persons of normal weight.
Adapted from "Preventing and Managing the Global Epidemic of Obesity. Report of the World Health Organization Consultation of Obesity." WHO, Geneva, June 1997.

The prevalence of obesity in the U.S. has increased more than two-fold since the 1970's. Currently, approximately one-third of Americans are clinically obese. Although the percentage of obese insurance applicants may not be quite that high, it is realistic to assume that a significant segment of insurance applicants are also obese.

Obesity is associated with a variety of health consequences that can unfavorably impact one's health and longevity. The most critical mortality considerations are hypertension,

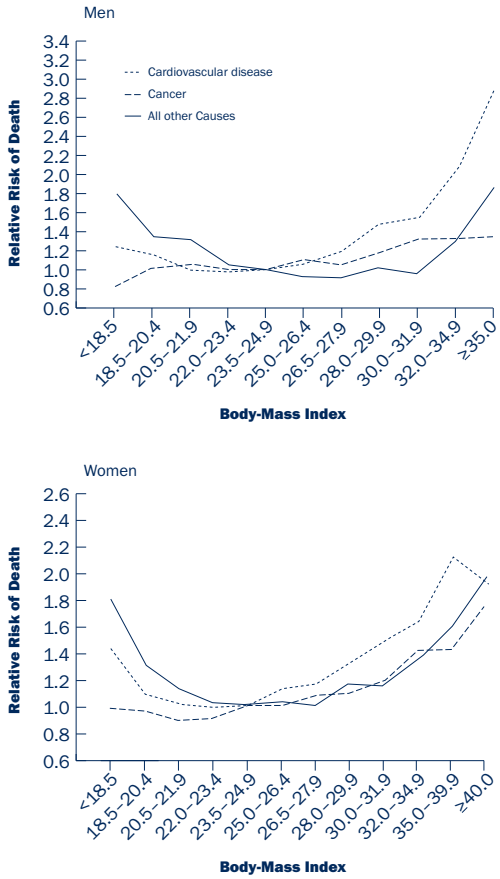
Age-adjusted* prevalence of overweight and obesity among U.S. adults, age 20–74 years



*Age-adjusted by the direct method to the year 2000 U.S Bureau of the Census estimates using the age groups 20–39, 40–59, and 60–74 years.

dyslipidemia, type 2 diabetes, coronary artery disease, congestive heart failure and stroke. The central theme of all of these concerns is the risk for, or the actual presence of, cardiovascular disease.

The relative risk of death (from all causes) by body mass risk in the general population was published in the New England Journal of Medicine (NEJM).



Multivariate Relative Risk of Death from Cardiovascular Disease, Cancer, and All Other Causes among Men and Women Who Had Never Smoked and Who Had No History of Disease of Enrollment, According to Body-Mass Index. The reference category was made up of subjects with a body-mass index of 23.5 to 24.9.

Tables 1 and 2 show the values of the low and high ends of the 95 percent confidence intervals of the pulmonary artery systolic pressure for men and women divided into age groups and body mass index (BMI) level groups. In the tables "n" is the number of subjects in each group and PSAP refers to Pulmonary Systolic Artery Pressure. It would be interesting to have normal values for different age groups with various weights, but the number of people in each group was not sufficient to allow valid data collection for each age/weight group.

A cursory look at the tables shows that the normal range of pulmonary artery pressure goes much higher than what is currently deemed acceptable in routine underwriting practice. It is reassuring that these results were confirmed in a letter to the editor of circulation from Milani et. al. at the Oschner Clinic in Louisiana. This group also compiled a similar very large listing of normal trans-thoracic echocardiograms and found similar results to those published by McQuinlan et. al.

TABLE 1

Normal Pulmonary Artery Systolic Pressure and Age 95% Confidence Interval Range, Low to High			
		Women (n=2065)	Men (n=1147)
Age, Years	n199	PSAP, mm Hg 95% CI	PSAP, mm Hg 95% CI
<20	856	18.6, 34.2	18.2, 36.2
20 to 29	669	19.2, 34.4	19.9, 36.3
30 to 39	650	19.3, 35.7	18.7, 37.5
40 to 49	494	19.9, 37.5	19.1, 38.3
50 to 59	344	20.2, 39.4	21.0, 40.6
60 and over	199	20.5, 42.1	21.2, 43.6

TABLE 2

Normal Pulmonary Artery Systolic Pressure and Body Mass Index 95% Confidence Interval Range, Low to High			
		Women (n=2065)	Men (n=1147)
BMI	n199	PSAP, mm Hg 95% CI	PSAP, mm Hg 95% CI
<20	645	19.9, 35.5	17.4, 36.2
20 to <25	1464	19.4, 35.8	18.9, 37.7
25 to <30	753	19.3, 37.7	19.7, 37.7
30 to <35	241	19.7, 40.1	20.5, 40.9
35 and over	95	21.4, 40.2	17.8, 40.6

It should be emphasized that these results be taken with caution, particularly in cases where additional disorders are implicated as causing pulmonary hypertension. Cases with COPD, OSA, Collagen Vascular Disease (particularly those with CREST syndrome or Raynaud's), thromboembolic disorders, and valvular heart disease must be underwritten with additional care.

Once a pathological form of pulmonary hypertension is present, the disease may become progressive, and the mortality associated with it is high. Review of the literature reveals that treatment for this disorder is generally not effective, and that advanced cases may require a heart-lung transplant for potential survival. One study delineating indicators for the need of a heart-lung transplant is from Hinderliter, et. al. that studied 81 patients with severe pulmonary hypertension. After 36.9 months follow-up, 20 patients had died, and 21 had undergone heart-lung transplants. Several echo findings indicating need for transplant were identified in this study. Pericardial effusion, anomalous septal displacement in systole, and severe right atrial enlargement were used as criteria for transplantation.

Behlm studied cases presenting with severe tricuspid regurgitation by echocardiography. This condition is mostly associated with severe PH and ischemic cardiomyopathy. The study showed the tricuspid valve itself was not damaged (86 percent of the cases by autopsy), and that severe tricuspid regurgitation is caused primarily by right-sided heart failure and pulmonary hypertension. Out of 77 patients in this study, 37 died within one year, and 17 of those within one month of the study.

The two prior studies are presented to help define objective indicators of severe pulmonary hypertension with extreme risk of mortality. PH in association with the findings described in these two studies is a cause to decline coverage.

This article presents some available research data indicating that the range of normal pulmonary artery systolic pressure may be higher than expected, and will vary with age and weight. The need for conservative underwriting of this disorder in combination with other common conditions like COPD and Collagen Vascular Disease is emphasized. In addition, some of the objective findings associated with a higher risk of mortality and poor prognosis for advanced pulmonary hypertension have been presented. It is hoped this information will help when underwriting cases with echos mentioning elevated pulmonary artery pressures.

INFORMATION

Find current and past issues of *Re-flections* at www.rgare.com/media/re_flections.asp

Classification of Pulmonary Arterial Hypertension

Pulmonary arterial hypertension:

- Primary (genetic, familial, sporadic)
- Related to systemic disorders (collagen vascular disease, congenital shunts, portal hypertension, HIV, drug toxicity)

Pulmonary venous hypertension:

- Left-sided heart disease/valvular disease
- Pulmonary venous occlusive disease
- Extrinsic compression of the pulmonary veins (mediastinitis, tumors)

Pulmonary hypertension due to respiratory disease or hypoxemia:

- Chronic Obstructive Pulmonary Disease (COPD)
- Sleep apnea with hypoxemia
- Alveolar hypoventilation disorders

Pulmonary hypertension resulting from chronic thrombotic or embolic disease:

- Thrombosis of the pulmonary arteries
- Pulmonary embolism
- Hemoglobinopathies (β Thalassemia, Sickle Cell)

Pulmonary hypertension resulting from disorders directly affecting the pulmonary vasculature:

- Pulmonary capillary hemangiomas
- Inflammatory lung disorders
- Schistosomiasis
- Sarcoidosis

Primary pulmonary hypertension (PPH) is a genetic-mediated disorder with incomplete penetrance, but with a relentless progression ending in early death. This is a very rare form of PH. Only 24 families have been identified as having the primary/familial form of this disorder, and 114 families have the sporadic form of the disorder (Simmoneau, 2004). There are genetic differences in these forms of PPH, but the end result for those patients manifesting the clinical disease is the same. Although this is a very rare form of the disease and the chances of underwriting any such cases are extremely slim, PPH patients are, of course, not insurable.

Much more common are the forms of PH associated with other disorders, and this is where the magnitude of the underwriting problem becomes evident, because a vast range of common disorders are associated with the development of pulmonary hypertension. Underwriters see a large number of cases with disorders causing hypoxia (Obstructive Sleep Apnea, COPD), and Thrombosis/Deep Venous Thrombosis. Many cases with valvular heart disease, collagen vascular disorders, hemoglobinopathies and sarcoidosis also present for underwriting. All of these conditions can produce significant pathological pulmonary hypertension and therefore may pose a much higher mortality risk than is commonly associated with them. Finding an elevated pulmonary artery pressure in association with these disorders should indicate the need for a more conservative rating or even a decline depending upon circumstances.

Central Issues Involved in Underwriting Pulmonary Hypertension

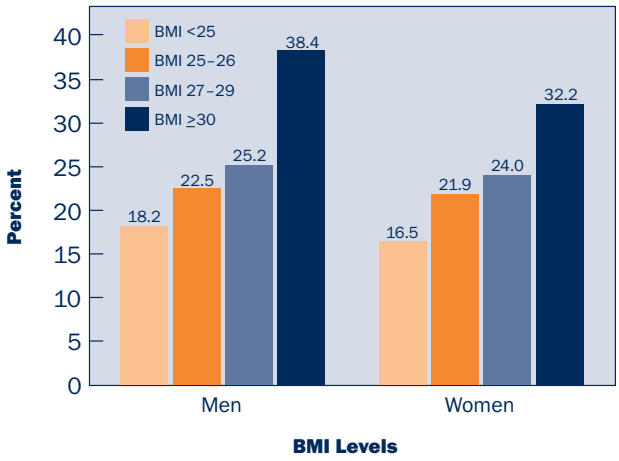
It is clear that underwriters are receiving an increasing number of echocardiograms showing elevated pulmonary artery pressures. The question is how to deal with these "abnormal" values; how to separate the higher mortality risks from those with acceptable levels of PH. McLaughlin stated: "Although idiopathic pulmonary arterial hypertension is perceived as a progressive disease with a uniformly poor outcome, the natural history of the disease is heterogeneous, with some patients dying within months of diagnosis and others living for decades." Fortunately, there has been some work done to establish the normal baseline levels of pulmonary artery pressure. The results of these studies are surprising in many ways, as discussed below.

In 2001, McQuinlan, et. al. published a study establishing reference values for pulmonary artery pressures determined by standard trans-thoracic echocardiograms. This study was based upon a database of 102,818 echocardiograms of which 15,596 were normal according to very strict criteria. In order to estimate pulmonary artery pressure, some degree of tricuspid regurgitation is required. Of these subjects with normal echos, 3,790 had enough tricuspid regurgitation to obtain a peak tricuspid regurgitant jet velocity measurement usable for a calculation of their pulmonary systolic artery pressure. Once tabulated, the results of this study showed that normal pulmonary artery systolic pressure rises with age and with increasing weight. When expressed within a 95 percent confidence interval (two standard deviations from the mean value), the results are striking.

These graphs clearly show that the obese population, particularly the morbidly obese, are at greater risk of dying than the non-obese. The NEJM data also suggests that males may be more affected by the negative health consequence of obesity than females. Presumably, this could be due to the high incidence of hypertension and dyslipidemia in the male population. From an insurance perspective, although this table is useful, it does not adequately address the insurance population, where it is possible to select out the uninsurable risks, or to risk select from within any particular BMI subset.

Risk selection is a cornerstone of life insurance underwriting, and with an increasing understanding of the relationship between obesity and cardiovascular risk, it may be possible to construct rational ratings tables for obesity that consider this condition as a single impairment or condition. Such a table would consider the mortality consequences of obesity as an independent risk factor for premature death. In essence, it would consider the mortality of an obese applicant that does not already have coronary artery disease, peripheral vascular disease, type 2 diabetes, significant hyperlipidemia or hypertension. These 'best-risk' obese applicants would likely have somewhat better mortality patterns than the non-screened obese general population. The assumption is that the up-sloping graph lines representing relative risk of death would be considerably flatter than that published in the NEJM. These graphs were developed based on mortality studies involving more than one million participants in the Cancer Prevention Study II. This population was studied from 1982 until 1996. One subset within this group was formed of non-smokers with no history of disease. This group was defined as people without a history of cancer, heart disease, stroke, chronic respiratory disease, current illness or a weight loss of at least 10 pounds in the previous year. There was no specific mention of diabetes, hypertension or hyperlipidemia being excluded from this group. This is important, since the mortality ratios were higher in this group than in the other subsets and this needs to be rationalized. Another consideration when viewing these results is the effect of the changes in treatments for hypertension, diabetes and cardiovascular disease that have occurred since the early 1980s.

NHANES III Age-Adjusted Prevalence of Hypertension* According to Body Mass Index

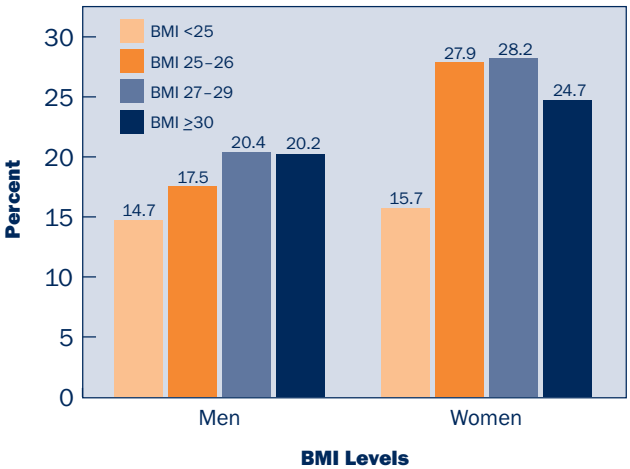


*Defined as mean systolic blood pressure ≥140 mm Hg, mean diastolic as ≥90mm Hg, or currently taking antihypertensive medication.

Source: Brown C. et al. Body Mass Index and the Prevalence of Risk Factors for Cardiovascular Disease (submitted for publication).

As BMI increases, the prevalence of hypertension and HDL/cholesterol ratios also rise (see table above). This is similarly true, although to a lesser extent, of hypercholesterolemia (see table below). The rise in mortality ratios among the 'healthy' obese (noted with rising BMI) may be at least partially explained by the rising incidence of these known cardiovascular risk factors. Likewise, the increasing incidence of diabetes among the very obese may also be a factor. This possibility was not adequately explored in the NEJM study. It is important to determine if the unfavorable mortality associated with obesity is due to obesity as an independent risk factor, or merely reflects the increased incidence of other cardiovascular factors among this population.

NHANES III Age-Adjusted Prevalence of High Blood Cholesterol* According to Body Mass Index



*Defined as ≥240 mg/dL

Source: Brown C. et al. Body Mass Index and the Prevalence of Risk Factors for Cardiovascular Disease (submitted for publication).

Obesity in general is associated with increasing levels of hypertension and dyslipidemia, and the use of paramedical assessments and lab testing can evaluate whether the specific obese applicant has these risk factors for cardiovascular disease. It is not clearly established whether obese people with normal lipids and normal blood pressure are still at risk of cardiovascular complications. Studies such as the Women's Ischemia Syndrome Evaluation (WISE), published in the JAMA in September 2004, suggested that obesity may not be an independent risk factor for excess death (at least in women), but this remains to be validated. The study suggested that "higher self-reported physical fitness scores were independently associated with fewer CAD risk factors, less angiographic CAD and lower risk for adverse CV events. Measures of obesity were not independently associated with these outcomes. These measures of obesity were BMI, waist circumference, waist-hip ratio, or waist-height ratio."

Other studies reached somewhat different conclusions, however. The Nurses' Health Study demonstrated that "higher levels of physical activity appeared to be beneficial at all levels of adiposity but did not eliminate the higher risk of death associated with obesity." The study also stated that "both increased adiposity and reduced physical activity are strong and independent predictors of death" (NEJM 351;26 December 23, 2004).

Better Understanding Obesity

Scientists have developed a clearer understanding of the role of the fat cell, or adipocyte, in the development of atherosclerosis. In the past, the adipocyte was often thought of as a relatively inert collection of lipids within a cell wall. It is now believed to be much more metabolically active, and through secreted cytokines it contributes to the inflammatory process in coronary arteries that eventually leads to production of vulnerable plaques and obstructive coronary artery disease.

Increased knowledge of the risks associated with obesity has led to a concerted effort among clinicians to reduce cardiovascular deaths. With the increasing use of the Statin class of drugs to reduce lipid levels and coronary artery inflammation, as well as anti-hypertensive drugs, it would be reasonable to expect to see a decline in the death rate among the obese population when compared to historical levels. This appears to be happening, as evidenced by an April 2005 news release from the CDC which stated that the prevalence of elevated cholesterol and blood pressure dropped by nearly half in all U.S. adults aged 20–74. The release also noted that "reductions in the prevalence of high cholesterol levels were most substantial among obese people compared to lean individuals."

There is no disputing the fact that the prevalence of obesity in America has risen over the last 50 years and may very well continue for some time, but the impact of obesity on mortality may have decreased over time, perhaps due to improvements in public health and medical care. These findings are consistent with the increases in life expectancy in the United States and the declining mortality rates from ischemic heart disease (JAMA 2005; 293: 1861–1867). In addition, with the exception of diabetes, CVD risk factors have declined considerably over the past 40 years in all BMI groups. Although obese persons still have higher risk factor levels than lean persons, the levels of these risk factors are much lower than in previous decades (NHANES/NHANES I/ NHANES III/NHANES 1999–2000 & JAMA 2005; 293: 1868–1874).

Recently published studies suggest that, after applying the basic principles of risk selection, today's obese applicant may be a better mortality risk than his or her historical counterpart. I specifically refer to the use of laboratory parameters such as a lipid profile, blood pressure readings, family history and smoking profile. Additional factors such as favorable hs-C-Reactive Protein, ultrafast CTs and waist-hip ratios may also contribute to the selection of the better-risk obese population, with the specific intent of reducing the excess mortality risk from cardiovascular deaths. Some studies, such as the Nurses' Health Study, suggest that attention should also be given to the activity level of the obese applicant.

The Future of Obesity

Unless preventive health measures quickly result in changes in the eating habits and physical activity levels of the American public, it is reasonable to assume that the prevalence of obesity will continue to rise. Inherently, this suggests that an increasing number of insurance applicants will need to be rated for this condition, even accounting for the improvements in mortality within the obese population. Fortunately, underwriters have the risk selection tools to differentiate the healthy obese from those at higher risk of developing the serious sequelae associated with obesity. The most problematic segment of the obese population is the young obese applicant, especially since these people are

at risk of developing early onset type 2 diabetes. Fortunately, there is also some evidence to suggest that the incidence rate of cardiovascular disease among adult diabetics is falling (JAMA, November 24, 2004 Vol. 292, No. 20). Hopefully, increasing knowledge of diabetes, and aggressive management of the disease, will mitigate some of this risk.

Some concerns have been voiced that the obesity 'epidemic' may actually reverse the gains in longevity that were made in the 20th century. Within socio-economically stable first world countries, the great epidemics of the 20th century including influenza outbreaks, coronary artery disease, and smoking-associated cancers, were not able to outstrip the mortality gains provided by improvements in sanitation, immunization, smoking reduction, pharmaceutical innovations and advances in medical treatments. While it is fair to be concerned about the negative impact of the growing prevalence in obesity, since it may produce a 'drag' on future longevity gains, there is reason to hope that the gains to be anticipated from medical research such as gene therapy alone may be substantially higher.

UNDERWRITING PULMONARY HYPERTENSION

by Oscar Cartaya, M.D.

Pulmonary hypertension is a disorder associated with a very high mortality rate. It is also, unfortunately, a disorder that is very difficult to evaluate. This article will review some of the recent information gathered about pulmonary hypertension, and suggest a valid framework for evaluating these cases.

Pulmonary hypertension (PH) has received a great deal of attention since D'Alonzo et. al. at the National Institutes of Health (NIH) published an article in 1991 on a series of 194 patients followed between 1981 and 1987. The article documented a life expectancy for these patients of only 2.5 years from the time of diagnosis. While the life expectancy in this study was very poor, there is mounting evidence suggesting that these findings are not indicative of all patients with PH. The patients in the NIH study were all suffering from advanced, symptomatic forms of PH. They were diagnosed by cardiac catheterization and had evidence of right-sided heart problems. This is not the common type of case presented to underwriters, which has a generally milder clinical picture. Patients with advanced pulmonary hypertension are uninsurable.

Underwriters typically evaluate cases where a patient has elevated pulmonary systolic pressures that are determined by trans-thoracic echocardiography, and are generally asymptomatic. These cases do not necessarily demonstrate the same severe mortality found in the NIH study. The challenge underwriters face is determining a way to evaluate such cases, and to establish valid underwriting guidelines to deal with pulmonary hypertension.

Pulmonary hypertension is a physiologic reaction to a variety of factors. Physiologically, elevation in the pulmonary arterial pressure is a compensatory mechanism triggered to maintain a steady level of oxygenation of the blood reaching the left ventricle. Any condition that increases blood flow or resistance through the pulmonary vasculature will increase pulmonary arterial pressure. Transient, physiological increases in pulmonary arterial pressure occur from exercise and high altitude.

Vigorous exercise causes cardiac output to increase, thus increasing the blood flow through the pulmonary circulation, which increases the pulmonary arterial pressure. During exercise, these effects are counterbalanced to some degree by pulmonary vasodilation, which opens up a greater amount of surface area for gas exchange in the alveoli. The net result of these changes is an increase in the amount of oxygenated blood available for circulation, and a net increase in the pulmonary artery pressure. A physiological increase in pulmonary arterial pressure (pulmonary vasoconstriction) can also result from high altitude with a decrease in atmospheric oxygen availability. In both of these examples, when the exercise ceases or the person descends to a lower altitude (with normal atmospheric oxygen levels), the pulmonary artery pressures return to normal. Transient elevations of pulmonary artery pressure are a part of normal compensatory mechanisms and have no associated increased risk of mortality.

Permanent elevations of pulmonary artery pressure are pathological and must be accounted for in underwriting practice. The problem underwriters face is that the distinction between what is physiologic and what is pathologic is somewhat blurred. To state it simply, final answers as to what constitutes pathologic elevations of pulmonary artery pressure are not fully defined at this time. However, since the 1991 NIH article, extensive research has identified several important indicators of PH.

A number of common disorders contribute to the development of permanent pathological elevations of pulmonary artery pressure and are used as the basis for classifying pulmonary hypertension.

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